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RECOVERY AFTER STROKE: LONG TERM OUTCOME AND UPPER LIMB SOMATOSENSORY FUNCTION

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Jury

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TABLE OF CONTENTS

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GENERAL INTRODUCTION

The first part of this general introduction will describe the definition, aetiology, pathophysiology and prevalence of stroke. The second part will elaborate on recovery and the clinical picture of upper limb function in people with stroke. More specifically, an overview will be provided on the current knowledge about recovery after stroke, as well as on motor and somatosensory impairments in the arm and hand post stroke. Third, needs and challenges for research, based on current knowledge, will be summarized. In the last part of this general introduction an outline of the objectives, research questions and the framework of the doctoral thesis will be presented.

1. Definition, aetiology, pathophysiology and prevalence of stroke

Stroke is defined by the World Health Organization in 1970 as "rapidly developing clinical signs of focal or global disturbance of cerebral function, lasting more than 24 hours or leading to death, with no apparent cause other than that of vascular origin".[1] Recently, the American heart association and the American stroke association provided an updated definition of stroke for the 21st century being "an episode of acute neurological dysfunction presumed to be caused by ischemia or haemorrhage, persisting more than 24 hours or until death, based on neuropathological, neuroimaging, and/or other clinical evidence of permanent injury".[2] Two major mechanisms cause brain damage in stroke, namely ischemia and haemorrhage. Ischemic strokes represent up to 87% of all strokes and are caused by a thrombus or an embolus that occlude a cerebral artery.[3,4] Neuronal tissue located in the affected vascular territory is deprived from blood and subsequently from the necessary energy supply, leading to brain tissue damage. On the other hand, intracerebral haemorrhagic strokes represent 10% to 15% of all strokes and are caused by a rupture of a blood vessel, leading to compression of brain tissue from the expanding hematoma.[3,4]

In the core area of a stroke, the blood flow is severely reduced, and therefore the brain tissue is irreversibly damaged from the outset. The tissue in the region bordering the core area, known as the penumbra, is functionally impaired but able to withstand the reduction in blood flow, at least for some time after the initial insult.[3] Neuronal cells in this region remain metabolically active, but become functionally inactive due to the reduced blood flow. If the blood flow and oxygen delivery is restored within a few hours after the onset of stroke, neuronal cells in this region are potentially recoverable.[3] Rehabilitation post stroke strives to take advantage of neuroplastic processes during the recovery period of the brain injury, including the recovery of the penumbra and the reduction of oedema and diaschisis.[5] Diaschisis is functional loss in areas remote from the lesion but neuronally connected to it.[5] Risk factors for stroke are high blood pressure, diabetes mellitus, disorders of heart rhythm such as atrial fibrillation, elevated blood cholesterol levels, smoking, unhealthy diet, physical inactivity, and older age.[4]

Worldwide, the prevalence of stroke survivors is estimated at 33 million.[6] Each year, 15 million people suffer a new stroke, with 9 million being a first-ever stroke.[6,7] Of these 15 million people with a new stroke annually, 5 million decease immediately as a consequence of the stroke and another 5 million remain permanently disabled.[7] The incidence of stroke is declining in many high-income countries, largely as a result of better risk factor management. However, the absolute number of strokes continues to rise because of the ageing population.[7] If this trend continues, by 2030 there will be approximately 70 million stroke survivors.[6] Stroke is a leading cause of long-term disability all over the world, and therefore, considered as a major health burden globally.[4]

2. Recovery and upper limb function in people with stroke

2.1 Recovery after stroke

Recovery is a complex process that occurs through a combination of spontaneous processes and learning-dependent approaches, such as restitution and compensation.[8,9] Depending on the time after stroke onset, recovery can be divided into three stages: the acute, sub-acute and chronic phase post stroke. Although there is no exact consensus on the precise timeframe of the different stages, it is generally accepted that the acute stage comprises the first hours up to one week post stroke, which is then followed by the sub-acute phase. The chronic phase post stroke is considered to start at six months after stroke onset.

Following stroke, a variety of signs and symptoms occur, depending on the location of the brain lesion.[8,10] The International Classification of Functioning, Disability and Health (ICF) provides a useful framework for categorizing the different problems that might occur post stroke at the level of body structure and function, activities and participation.[11] Most commonly, patients experience unilateral muscle weakness, i.e. paresis or paralysis, in the face, arm or leg contralateral to the brain lesion. Additionally, an altered sensation or numbness in the face or limbs, speech disturbances and cognitive problems are often reported post stroke.[8,10] These affected body functions result in activity limitations such as walking, dressing and eating as well as restrictions in participation in the community.[8] In the literature, considerable agreement exists about the typical exponential pattern of recovery for impairments and disabilities up to six months post stroke, irrespective of the type and amount of therapy.[12,13] Most recovery is seen in the first weeks after stroke, with the recovery slope reaching a plateau between three and six months.[12,13] Time is an independent factor for recovery of body functions and activities in the first weeks and months post stroke, explaining up to 40% of the observed improvements.[14,15]

Long-term prospective cohort studies up to several years after stroke are scarce. Most studies are community-based and use only broad outcome measures, such as being functionally (in)dependent.[16] Detailed long-term motor and functional recovery patterns, measured up to several years after stroke rehabilitation, have received less attention. Several studies have shown that women have a less favourable outcome after stroke than men.[17,18] Furthermore, there is strong evidence that age and stroke severity are negatively associated with functional outcome after 3 months post stroke.[19,20] Another important factor influencing stroke recovery is stroke aetiology. Patients with intracerebral haemorrhagic strokes (ICH) have a higher risk of death and worse initial functional and motor performance compared to patients with ischemic strokes, but it is generally alleged that ICH survivors have better neurological and functional recovery during inpatient rehabilitation than patients having ischemic stroke.[21,22] Further studies are needed to investigate whether early improvements in motor and functional outcome gained during stroke rehabilitation, are maintained up to several years after stroke, and which patient characteristics influence long-term outcome.

Approximately 70% of stroke survivors experience impairments in the upper limb.[10,23] As a consequence, upper extremity functions, such as reaching, grasping, releasing and manipulating objects are hindered, often resulting in a non-use of the affected upper limb.[24] Dysfunction in the upper limb post stroke can therefore significantly limit a person's level of activity and participation and warrants further consideration in stroke rehabilitation research. The next sections of this general introduction will look in detail into motor and somatosensory impairments in the upper limb, because it is well established that sensory information contributes to the control of movement at the level of the spinal cord and through the ascending pathways up to the cerebral cortex.[25,26] In this view, the somatosensory system plays a crucial role in movement as it provides information about the current state of the body segments to plan actions and to correct on-going movements if they are inaccurate or if a perturbation occurs.[25,26] Although an intact somatosensory functioning is important for motor control in healthy subjects,[5,25-27] it remains unclear to what extent somatosensory impairments following stroke are related to motor impairments in the upper limb, and whether the strength of this association changes over time.

2.2 Motor impairment post stroke

Upper limb motor impairment is one of the most common symptoms post stroke, and consists of muscle weakness, a decreased ability to perform selective movements and loss of dexterity.[10,23,28] Therefore, relearning specific motor skills and functional daily tasks is one of the main goals in stroke rehabilitation.[27,28]

Although a clear exponential pattern of recovery has been described,[12-13] it is well recognized that there is high inter-individual variability in the extent of upper limb recovery in the first six months post stroke.[23,29,30] Different longitudinal studies[23,29,30] indicate that at six months post stroke, 30% to 66% of patients with stroke still have a non-functional arm and hand, whereas only 5 to 20% regain complete upper limb function.[29] Two recent systematic reviews[31,32] summarizing the prognostic variables relating to upper limb recovery post stroke, showed that initial motor impairment was the most important predictive factor for upper limb recovery. The EPOS cohort study[33] showed that presence of finger extension and shoulder abduction within 72 hours after stroke predicts dexterity at six months post stroke. Prabhakaran and colleagues[34] developed a proportional recovery model, suggesting that the amount of spontaneous motor recovery of the upper limb is relatively fixed at approximately 70% of patients' maximal potential recovery. However, a recent study[35] showed that approximately 30% of the stroke survivors had significantly less improvement than predicted. These non-fitters had more severe neurological impairment in the first 72h post stroke. The absence of finger extension, the presence of facial palsy, more severe lower limb paresis and a more severe type of stroke according to the Bamford classification, were significant predictors for non-fitting the proportional recovery model.[35]

Severity of upper limb motor impairment is often greatest in distal muscles and least in proximal shoulder muscles.[36] However, the ability to perform purposeful movements requiring precise control of the proximal muscles for reaching as well as of the distal muscles for grasping is disrupted in people with stroke. The movements are overall slower, less accurate and less coordinated compared to healthy adults.[37,38] In a study of Lang et al.,[39] relative deficits in reaching versus grasping were evaluated by converting performance in movement speed, accuracy and efficiency to z-scores using control group means and standard deviations. It was shown that the ability to perform movements with the distal segments was not clearly more disrupted than the ability to perform movements with the proximal segments in acute stroke.[39]

Recently, a mismatch between upper limb functional performance and self-reported perceived hand function was identified.[40,41] These studies showed that the perceived disability measures captured hand function problems that were not assessed by the performance scales. The level of education and mood significantly influenced the relationship.[40] This highlights the need for combining both performance and self-perception measures in clinical practice to evaluate upper limb rehabilitation after stroke.[40,41] Furthermore, these studies indicate that restoration of everyday use of the upper limb is not only dependent on motor recovery, but other unmeasured factors such as somatosensory impairments might contribute to the perceived disability of the upper limb in daily practice.

2.3 Somatosensory impairment post stroke

Somatosensation is a broad term covering all sensory information arising from the skin, muscles and joints, which is transferred through the peripheral and central nervous system, up to the cerebral cortex. It is different from visceral or internal sensations such as the feeling of your heartbeat, and the special senses such as hearing, seeing, smelling, or tasting.[42] In the following part, the current knowledge on somatosensory modalities, the afferent somatosensory tracts and important brain regions for somatosensory processing will be elaborated in detail. Subsequently, different assessment methods and the prevalence of different somatosensory deficits in the upper limb post stroke will be discussed and finally, the impact of upper limb somatosensory impairments on outcome post stroke will be presented.

Somatosensory modalities

Somatosensory functioning can be broadly classified into exteroceptive, proprioceptive and higher cortical somatosensory function.[43] Exteroceptive and proprioceptive function are the so-called primary somatosensory functions, whereas the higher cortical somatosensory function is a combined, higher-order function. For the latter, an intact primary somatosensory function is required; the ability to feel the stimulus is a prerequisite for the ability to discriminate between stimuli. Each of the three somatosensory functions encompasses different modalities, as listed in Table 1.[43] Exteroceptive function comprises the ability to detect light touch, pressure, pinprick and temperature. Proprioceptive function consists of position sense, movement sense and vibration sense. Finally, higher cortical somatosensory function consists of somatosensory discrimination such as the ability to discriminate between sharp and dull stimuli, between different objects (stereognosis), between numbers written on the skin (graphesthesia) and between one or two stimuli (two-point discrimination).[43]

Table 1. **Overview of different somatosensory modalities in the classification of exteroceptive, proprioceptive and higher cortical somatosensory functions** (according to Dejong, 1979[43])

Somatosensory function	Somatosensory modalities
Exteroception	Light touch
	Temperature
	Pinprick
	Pressure
Proprioception	Position sense
	Movement sense
	Vibration sense
Higher cortical somatosensation	Sharp-dull discrimination
	Stereognosis
	Graphesthesia
	2-point discrimination

Somatosensory tracts

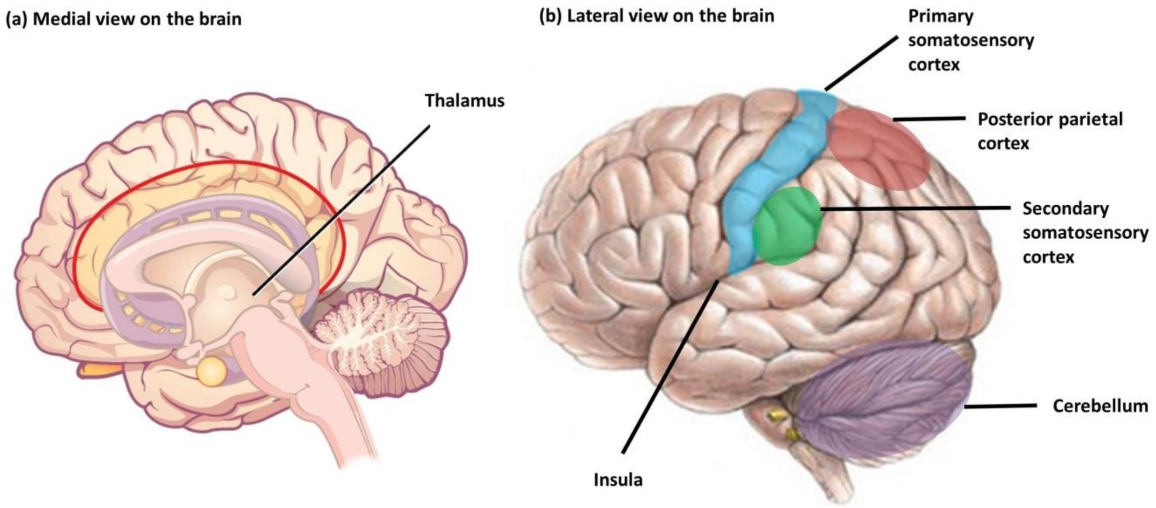
Sensory information from receptors in the skin, muscle spindles, Golgi tendon organs, joint capsules and ligaments are processed through the peripheral nervous system until it reaches the spinal cord. Three main afferent systems transmit specific somatosensory information in the spinal cord up to the brain: 1) the spinothalamic system, including a lateral and anterior spinothalamic tract; 2) the dorsal system including fasciculus gracilis and fasciculus cuneatus; and 3) the spinocerebellar system including a posterior and anterior spinocerebellar tract.[25,42] The spinothalamic system transmits exteroceptive information. In the spinal cord, most of the fibres of the spinothalamic tracts cross-over to the opposite site until they reach the contralateral thalamus, through the capsula interna up to the primary somatosensory cortex. Second, the dorsal system is responsible for proprioceptive information and fine discriminative touch, the latter upon the condition that the exteroceptive function is intact.

Somatosensory stimuli coming from the lower limb are transmitted through the fasciculus gracilis, and the fasciculus cuneatus is responsible for information coming from the upper limb. Sensory information is processed ipsilaterally in the spinal cord, until the tracts reach the medulla oblongata. Here both fasciculus gracilis and cuneatus merge together into one tract, the so-called lemniscus medialis, which crosses-over to the opposite site at the level of the medulla oblongata towards the contralateral thalamus, through the capsula interna up to the primary somatosensory cortex. Finally, the spinocerebellar system transmits information about unconscious proprioception. The anterior spinocerebellar tract is responsible for information coming from the lower limbs, whereas upper limb information is processed by the posterior spinocerebellar tract. For this latter tract, information is solely processed ipsilaterally in the spinal cord, and reaches through the pedunculus cerebellaris inferior the ipsilateral cerebellar hemisphere.[25,42]

Core brain regions

Once the somatosensory information reaches the brain, the information is processed in different brain regions, all contributing to somatosensory processing.[25,42,44] The core brain regions include the thalamus, primary somatosensory cortex (S1), secondary somatosensory cortex (S2), insula, posterior parietal cortex (PPC) and the cerebellum. Figure 1 shows the anatomical location of the different core brain regions.

Figure 1. Core brain regions in somatosensory processing



Adapted from philschatz.com/biology-book, www.imagekb.com/brain

The **thalamus** is a key brain structure in somatosensory processing. Somatosensory information from the periphery enters the thalamus in the ventroposterior area. The thalamus has connections to both S1 and S2, the PCC and the insula. The anterior cingulate makes interhemispheric connections between the bilateral thalami.[25,42,44] Second, the **primary somatosensory cortex (S1)** is located posterior to the central sulcus in the parietal cortex. S1 includes Brodmann area's 1, 2, 3a and 3b, and is mainly involved in the detection of somatosensory stimuli, and remains largely modality-specific. For example, Brodmann area's 1, 2, and 3b would process more exteroceptive information, whereas Brodmann area's 2, and 3a have been previously associated with proprioceptive function. S1 has projections to S2, the primary motor cortex and supplementary motor area.[25,42,44] Third, the **secondary somatosensory cortex (S2)** has a role in somatosensory discrimination, and is located in the parietal operculum. Somatosensory information is less modality-specific in S2 compared to S1. S2 has reciprocal connections with both thalamus and S1, and has also projections to the premotor cortex.[25,42,44] Additionally, the **insula** is a somatosensory association area which plays also a major role in the recognition and higher order interpretation of somatosensory stimuli.[42,44] Furthermore, the **posterior parietal cortex (PPC)** receives projections from both S1, S2 and the thalamus and projects back to the premotor cortex and S2. This brain region is identified as core brain region for the integration of somatosensory information with information from other senses such as the visual system, to guide motor action.[25,44] Finally, the **cerebellum** plays an important role in unconscious proprioceptive processing and is connected to the contralateral somatosensory cortical network.[25,44]

In contrast to the large amount of studies reporting on neural correlates of motor impairments after stroke,[45-47] the relationship between lesion location and somatosensory deficits after stroke remains poorly understood. Lesion inference studies of somatosensory deficits may add to the understanding of the disturbed brain function post stroke. Recent evidence showed that reduced structural connectivity of the superior thalamic radiation, connecting the thalamus to S1, using diffusion tensor imaging in chronic stroke patients, was associated with tactile dysfunction and impairments in tactile discrimination.[48,49] Up to now, studies in the acute phase post stroke using this technique are missing.

Another new promising technique called voxel-based lesion-symptom mapping, allows identification of brain areas responsible for specific functions, and thus provides the opportunity to link clinical symptoms with affected brain areas. To date, only two studies investigated the voxel-wise association between lesion location on magnetic resonance imaging in people with stroke and a resulting somatosensory deficit.[50,51] It was found that impaired light touch perception in the chronic phase post stroke was associated with lesions in S2, the anterior and posterior insular cortex, the putamen, and white matter connections reaching ventrally towards prefrontal brain areas.[50] The other voxel-wise association study, including chronic patients with insular strokes, demonstrated that lesions in the posterior insular cortex are associated exclusively to impaired temperature perception.[51] Lesion inference studies of different somatosensory modalities has not been conducted as yet using modern voxel-based imaging methods. Thus, it remains unclear to what extent lesions in these brain areas affect other sensory modalities besides light touch and temperature perception, especially in the acute phase post stroke. Results from functional brain imaging studies investigating activation patterns during sensory stimulation is outside the scope of this general introduction, and will be discussed in the general discussion.

Somatosensory assessment

Quantitative and precise measurement of somatosensory function after stroke is crucial in order to evaluate the impairment, to set treatment goals, and to evaluate treatment efficacy. A recent study of Pumpa et al.[52] showed that most physical and occupational therapists working with stroke survivors, routinely assess somatosensory impairments, but with the majority not using standardised measures. Despite published evidence regarding standardised and reliable somatosensory assessment, an evidence-practice gap was identified.[52] In clinical practice, somatosensory impairments are often measured using clinical bedside tests[53], such as striking the skin with a cotton wool to assess light touch or hot and cold water tubes to assess temperature sense. Position sense is in clinical practice often assessed using the thumb finding test or by asking the patient to mirror the position of the affected upper limb, with the non-affected side. For the graphesthesia assessment, the assessor writes numbers with a spatula on the hand of the patient, whereas for stereognosis, different common objects need to be identified by only touching the objects, while blindfolded.[53]

Although these tests are useful to gain an indication of impairments, they are not standardised, information about reliability and validity is missing, and consequently it is not possible to evaluate treatment efficacy.

In clinical guidelines, the use of standardised measures is explicitly stated to be crucial.[54,55] However, 'gold standard' measures are often lacking, which is a barrier for the use of standardised measures in clinical practice. A systematic review by Connell and Tyson[56] evaluated the psychometric properties and clinical utility of different measures of somatosensation. Clinical utility was assessed by the time to complete the test, the evaluation of costs, portability and specialized equipment. The psychometric properties that were assessed are concurrent validity, test-retest and inter-rater reliability and the ability to detect change. This review showed that the Erasmus-modifications of the Nottingham sensory assessment (Em-NSA), the stereognosis section of the original Nottingham sensory assessment (NSA) and the sensory section of the Fugl-Meyer assessment showed the best balance between clinical utility and psychometric properties.[56]

Besides the pure clinical standardized somatosensory outcome measures, there are also more quantitative measures of somatosensation such as the perceptual threshold of touch, Semmes-Weinstein monofilaments or somatosensory evoked potentials. The perceptual threshold of touch[57] is the minimal stimulus level of touch that is detectable. A transcutaneous electric nerve stimulation (TENS) is applied to the index finger with a high-frequency constant current of 40 Hz with single square pulses of 80 µs pulse duration. The amplitude is gradually increased, until a tingling sensation is perceived. This high-frequency TENS activates the receptors for light touch, and therefore the exteroceptive function can be measured accurately. The Semmes-Weinstein monofilaments are different nylon monofilaments of increasing diameters which can be applied on the skin until the monofilament bends. The increasing diameter of the monofilaments result in a progressive increase in pressure needed to bend the filament, and therefore the pressure perception can be measured in a quantitative way.[58] Somatosensory evoked potentials (SSEP)[59] are a measure of the transmission of a sensory stimulus from a peripheral nerve through the dorsal column up to the primary somatosensory cortex. Therefore, a transcutaneous electrical stimulation is delivered to the median nerve at the wrist with a pulse of 200 µsec and a stimulation rate of 5.1 Hz. Stimulation is performed at 3 times the sensory threshold, defined at the non-affected side, always above the motor threshold so that it produces a clearly visible muscle twitch causing abduction of the thumb. Electrical activity in the primary somatosensory cortex is measured through standard EEG electrodes, placed at positions CP3 and CP4 on the skull; according to the international 10-5 system.[60] Cortical amplitudes and latencies of the electrical signal can then be calculated.

Prevalence of upper limb somatosensory impairments post stroke

Somatosensory deficits in the upper limb are common post stroke,[61-68] with impairments in exteroceptive, proprioceptive and higher cortical somatosensory functions, but to date, information regarding the extent of deficits in all the different modalities in one cohort of patients is missing. Prevalence rates range from 23 to 55% for exteroceptive impairments,[61-66] from 19 to 64% for proprioceptive impairments,[61,63,65-67] and up to 89 % for higher cortical somatosensory deficits.[63,67,68] Differences in study populations, time post stroke, the somatosensory modality tested, and assessment method used, contributes to the variability in results.[69] Studies conducted until now generally assessed patients in the sub-acute to chronic phase post stroke. Only two studies[66,68] reported on the extent of somatosensory deficits assessed within the first week post stroke. Welmer et al.,[66] reported light touch deficits in 32% of patients and proprioceptive deficits in 41% of patients whereas Kim et al.,[68] found that 85% had impaired somatosensory discrimination sense in the first week post stroke. However, studies combining different standardized measures to map exteroceptive, proprioceptive and higher cortical somatosensory deficits in the different phases post stroke are missing.

Impact of upper limb somatosensory impairments and confounding factors post stroke

Several cross-sectional studies[64,70-72] conducted in the sub-acute to chronic phase, reported a significant positive association between somatosensory function and overall motor performance in the upper limb,[64,70] pinch grip,[71] and bimanual coordination.[72] However, most of these studies had restricted sample sizes of patients in the chronic phase post stroke and only in one study[70] different somatosensory modalities were assessed to look at the relationship with motor function. Furthermore, these studies included overall only mildly affected stroke patients, without aphasia, cognitive impairments or visuo-spatial neglect, which is an important consideration for the generalizability of these results.[64,70-72] Loss of somatosensory functioning post stroke has further been related to decreased independence during activities of daily living (ADL),[61] and impacts on the performance and satisfaction during valued activities.[62]

Interestingly, one study[66] assessed the importance of impairments in light touch and proprioception in the recovery of fine hand use in the different phases of the recovery process, namely in the first week, at three and 18 months in a sample of 66 patients after a first-ever stroke. The strength of the association between somatosensory functions and fine hand use, as assessed with the nine-hole peg test, changed slightly over time. A significant positive moderate association between fine hand use and both light touch (r=0.59) and proprioception (r=0.56) was reported in the first week after stroke. The strength of cross-sectional sensorimotor associations was r=0.56 and r=0.50 at 3 months, respectively. At 18 months post stroke, the strength of the association was r=0.46 for both the association with light touch and proprioception. However, it is important to notice that no standardized and reliable assessment methods for somatosensory functioning were used in this study, and patients were only classified as having normal or impaired light touch and proprioceptive function.[66] Furthermore, the authors computed Spearman rank correlations to assess the association between the continuous outcome on the nine-hole peg test and the dichotomized outcome for somatosensory functioning. However, this can be questioned, as the calculation of point-biserial correlation coefficients should be considered when addressing this relationship.[73]

Therefore, there is a need for high-quality cohort studies that combine reliable and valid somatosensory measures of different modalities to determine the relationship with motor and functional performance of the upper limb with more accuracy in the different phases of recovery post stroke. These insights are crucial for guiding and delineating future treatment interventions for upper limb sensorimotor deficits post stroke.

Furthermore, it is well known from literature that the presence of visuo-spatial neglect has a negative impact on motor recovery[74] and performance in activities of daily living.[75] Spatial neglect has been defined as the inability to detect, respond to, and orient towards novel and significant stimuli occurring in the hemi space contralateral to a brain lesion.[76] Despite the shared neuro-anatomy between somatosensory processing and the presence of visuo-spatial neglect in areas of the parietal cortex,[77-78] only a few studies[74,79-82] reported the relationship between visuo-spatial neglect, and somatosensation in the upper limb. The presence of visuo-spatial neglect seems to be associated with more severely affected limb position sense in the arm,[74,79-81] and is predictive for impaired limb movement sense.[82] However, information on the association between visuo-spatial neglect and exteroceptive or higher cortical somatosensory deficits after stroke is lacking.

3. Knowledge gaps in upper limb dysfunction post stroke

Notwithstanding the current efforts, research into upper limb function following stroke still has its restrictions. First, the recovery pattern of motor function is well described up to six months after stroke, but it remains unclear whether early improvements achieved during inpatient rehabilitation are maintained up to several years after stroke, and which patient characteristics influence long-term outcome. Second, up to now, prevalence studies of somatosensory deficits post stroke combining exteroceptive, proprioceptive and higher cortical somatosensory function are lacking. Third, although it has been reported that somatosensory impairments are related to a decreased ADL performance post stroke, it remains unclear how deficits in several somatosensory modalities in the upper limb are related to motor performance in the different phases post stroke, and whether neglect is a confounding factor in this relation. Finally, recent studies showed that impaired light touch perception was associated with lesions in S2, the insula, the putamen, and white matter connections reaching ventrally towards prefrontal brain areas, whereas impairments in temperature sense were associated with lesions in the posterior insular cortex. However, it remains unclear to what extent lesions in these brain areas affect other sensory modalities besides light touch and temperature perception. This doctoral project will address the above-mentioned gaps in knowledge. The objectives, research questions and outline of this project are presented in the next section.

4. Objectives, research questions and outline of the doctoral project

4.1 Objectives

The scope of this doctoral project is to provide more insights into recovery post stroke, in particular with regard to long-term outcome and somatosensory function in the upper limb.

The specific objectives are:

(1) to investigate the long-term time course of recovery post stroke;

(2) to give an overview of the existing evidence on the association between somatosensory deficits in the upper limb and outcome;

(3) to map the prevalence and distribution of different somatosensory deficits in the upper limb in a cross-sectional study, and to determine the association between somatosensory impairments and motor impairment and activity limitations, and to investigate whether neglect is a confounding factor;

(4) to map change over time in prevalence and distribution of different somatosensory deficits in the upper limb in a longitudinal study, and to determine the association between somatosensory impairments and motor impairment and activity limitations both in the acute and chronic phase post stroke;

(5) to investigate the relationship between stroke lesion location and the resulting somatosensory deficit in the acute phase.

4.2 Research questions

The following research questions are addressed in the doctoral thesis, according to the above-mentioned objectives:

Objective 1: long-term time course of recovery

- What is the long-term time course of motor recovery post stroke?
- Which patient characteristics influence long-term motor recovery?

Objective 2: overview of the existing evidence

- What is currently known about the association between somatosensory impairments in the arm and hand and upper limb motor impairments, activity and participation problems post stroke?

Objective 3: prevalence and distribution of somatosensory deficits and the association with motor impairment and activity limitations, and confounding of neglect

- What is the prevalence and distribution of different somatosensory impairments in the upper limb in the first six months post stroke?
- Is neglect an influencing factor for the prevalence and distribution of somatosensory deficits?
- How are different somatosensory deficits in the upper limb related to motor outcome and activity limitations?
- Is neglect an influencing factor for the relation between somatosensory and motor impairment?

Objective 4: change over time in prevalence and distribution of somatosensory deficits and in association with motor impairment and activity limitations

- What is the change in prevalence and distribution of different somatosensory impairments in the upper limb over time?
- Does the strength of the relation between different somatosensory deficits in the upper limb and motor impairment and activity limitations differ between the acute phase and at six months post stroke?

Objective 5: relationship between stroke lesion location and somatosensory deficits

- Which brain lesion locations are associated with somatosensory deficits in the upper limb in the acute phase post stroke?

4.3 Outline

The doctoral thesis consists of five studies, which are outlined in the paragraphs below, covering the specific objectives and research questions of this doctoral project. An overview of the research questions, study design, and time of measurement post stroke for each of the studies performed within this doctoral project, are provided in table 2. Detailed information regarding the study participants and the different outcome measures used, are provided in table 3.

In **Chapter 1**, results of a longitudinal observational cohort study are reported, in which 532 patients with stroke were included. Patients were assessed on admission to the rehabilitation centre, at two months, at six months and at five years post stroke. In this study we analysed the long-term motor recovery between admission to a rehabilitation centre and five years post stroke, and secondly, we evaluated the influence of age, gender, stroke severity and stroke pathogenesis on long-term outcome.

Chapter 2 entails a systematic review of the current, available literature to identify, evaluate, summarize and critically appraise the literature regarding the association between somatosensory impairments in the upper limb and outcome after stroke. A summary of the results of the included studies is reported, according to the different outcome measures within the domains of the ICF model, namely body function, activity and participation.

In **chapter 3,** results of a cross-sectional observational study are reported, in which 122 patients with stroke were included within the first six months post stroke. First, the prevalence and distribution of different somatosensory impairments, including exteroceptive, proprioceptive and higher cortical somatosensory deficits were mapped for the total group and for patients with and without visuo-spatial neglect separately. Finally, the association between these different somatosensory impairments and motor and functional outcome in the upper limb was determined, and the influence of visuo-spatial neglect on this association was explored.

Chapter 4 includes results of a longitudinal observational study, in which 32 patients with stroke were assessed four to seven days post stroke, and again at six months. The prevalence and distribution of different somatosensory impairments, including exteroceptive, proprioceptive and higher cortical somatosensory deficits, were mapped, both within the first week after stroke and at six months. Furthermore, the association between different somatosensory impairments and motor impairment within the first week was determined. Finally, the association between different somatosensory deficits in the upper limb and motor impairment and activity limitations at six months was investigated.

Finally, in **chapter 5**, the results of a cross-sectional observational study are reported, in which 38 patients with stroke were assessed four to seven days post stroke. Besides the assessment of exteroceptive and proprioceptive function in the upper limb, patients underwent an MRI brain imaging protocol. Non-parametric voxel-based lesion-symptom mapping was performed to investigate the lesion contribution to different somatosensory deficit in the upper limb. Additionally, structural connectivity of brain areas that demonstrated the strongest association with somatosensory symptoms was determined, using probabilistic fibre tracking based on diffusion tensor imaging data from a healthy age-matched sample.

The doctoral thesis is concluded by a **general discussion**, in which the main findings of the doctoral project are summarized and interpreted, critical considerations are discussed and recommendations for clinical practice and future research are proposed.

Table 2. Overview of the outline of the doctoral thesis

	Research Questions	Study design	Measurement time point
Chapter 1	➢ What is the long-term time course of motor recovery post stroke? ➢ Which patient characteristics influence long-term motor recovery?	Longitudinal observational cohort study	Admission to rehabilitation centre 2 months post stroke 6 months post stroke 5 years post stroke
Chapter 2	➢ What is currently known about the association between somatosensory impairments in the arm and hand and upper limb motor impairments, activity and participation problems post stroke?	Systematic review	-
Chapter 3	➢ What is the prevalence and distribution of different somatosensory impairments in the upper limb in the first six months post stroke? ➢ Is neglect an influencing factor for the prevalence and distribution of somatosensory deficits? ➢ How are different somatosensory deficits in the upper limb related to motor outcome and activity limitations? ➢ Is neglect an influencing factor for the relation between somatosensory and motor impairment?	Cross-sectional observational study	< 6 months post stroke
Chapter 4	➢ What is the change in prevalence and distribution of different somatosensory impairments in the upper limb over time? ➢ Does the strength of the relation between different somatosensory deficits in the upper limb and motor impairment and activity limitations differ between the acute phase and at six months post stroke?	Longitudinal observational cohort study	4-7 days post stroke 6 months post stroke
Chapter 5	➢ Which brain lesion locations are associated with somatosensory deficits in the upper limb in the acute phase post stroke?	Cross-sectional observational study	4-7 days post stroke

Table 3. Overview of the study participants and methods used in the doctoral thesis

	Participants	Inclusion criteria	Exclusion criteria	Outcome measures used
Chapter 1	N = 532	➢ First-ever stroke ➢ Age 40 to 85 years ➢ Motor impairment according to: RMA-GF ≤11, RMA-LT ≤8, RMA-A ≤12	➢ Other neurological impairment ➢ Stroke-like symptoms with other cause ➢ Admission >6 weeks post stroke ➢ Prestroke Barthel Index score <50	➢ RMA-GF ➢ RMA-LT ➢ RMA-A ➢ Barthel Index
Chapter 2*	-	-	-	-
Chapter 3	N = 122 [+]	➢ First-ever stroke ➢ Age >18 years ➢ <6 months after stroke ➢ Motor and/or somatosensory impairment in the upper limb ➢ Substantial cooperation	➢ Other neurological impairment ➢ Stroke-like symptoms with other cause ➢ Prestroke Barthel Index score <95 ➢ Serious communication, cognitive or language deficits	➢ **Somatosensory assessment:** Em-NSA, Thumb finding test, PTT, Stereognosis – NSA, Two-point discrimination ➢ **Motor assessment:** FMA-UE, MI, ARAT ➢ **Activity limitation assessment:** Ad-AHA Stroke
Chapter 4	N = 32 [$]	➢ First-ever stroke ➢ Age >18 years ➢ 4-7 days after stroke ➢ Motor and/or somatosensory impairment in the upper limb ➢ Substantial cooperation	➢ Other neurological impairment ➢ Stroke-like symptoms with other cause ➢ Prestroke Barthel Index score <95 ➢ Serious communication, cognitive or language deficits	➢ **Somatosensory assessment:** Em-NSA, Thumb finding test, PTT, Stereognosis – NSA, Two-point discrimination ➢ **Motor assessment:** FMA-UE, MI, ARAT ➢ **Activity limitation assessment:** Ad-AHA Stroke, ABILHAND, Hand subscale of SIS
Chapter 5	N = 38	See chapter 4	See chapter 4	➢ **Somatosensory assessment:** Em-NSA, PTT, SSEP

* Chapter 2 was a systematic review of the literature, [+] Overlap of patients (n=21) in studies reported in chapter 3 and 4, [$] Overlap of patients (n=30) in studies reported in chapter 4 and 5, RMA-GF: Rivermead Motor Assessment of Gross Function, RMA-LT: RMA of Leg and Trunk function, RMA-A: RMA of Arm function, Em-NSA: Erasmus MC modification of the (revised) Nottingham sensory assessment, PTT: Perceptual threshold of touch, FMA-UE: Fugl-Meyer motor assessment upper extremity, MI: Motricity Index, ARAT: Action Research Arm Test, Ad-AHA Stroke: adult-Assisting Hand Assessment Stoke, SIS: Stroke impact scale, SSEP: Somatosensory evoked potentials

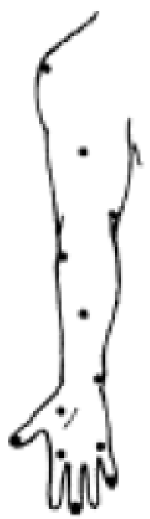
4.4 Somatosensory outcome measures used throughout the doctoral thesis

The somatosensory outcome measures used throughout the different studies of this doctoral thesis were chosen based on evidence provided in the literature regarding the psychometric properties and clinical utility of the different scales.[56] Additionally, as we wanted to provide a detailed overview of deficits in the different somatosensory modalities, we included a broad range of outcome measures covering these modalities.

Exteroceptive somatosensation

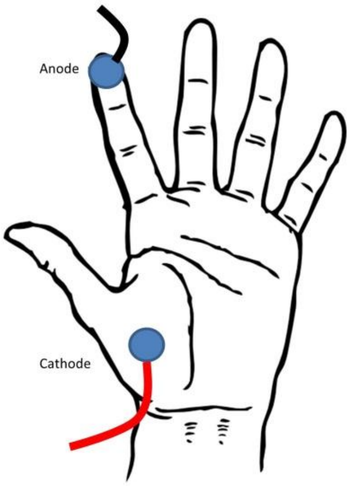
The Erasmus MC modification of the (revised) Nottingham sensory assessment (Em-NSA)[83] assesses light touch, pressure and pinprick. Light touch was applied with a cotton wool, pressure with the index finger and pinprick with a toothpick, at predefined points of contact (Figure 2). Scores for each modality range from 0 (loss of somatosensory function) to 8 (intact somatosensory function). A cut-off score of <7 indicates the presence of somatosensory impairment. The Em-NSA has good to excellent intra-rater and inter-rater reliability.[83]

Figure 2. Points of contact during Em-NSA assessment[83]



The perceptual threshold of touch (PTT)[57] is the minimal stimulus level of touch that is detectable. A transcutaneous electric nerve stimulation (TENS) was applied with a portable device: A CEFAR Primo Pro (Cefar Medical AB, Sweden). Round electrodes, with a diameter of 3 cm, were applied to the index finger and bulb of the thumb (figure 3). A high-frequency constant current of 40Hz with single square pulses of 80µs pulse duration is applied. The amplitude is gradually increased with increments of 0.5mA, until a tingling sensation is being perceived at the index finger. Good psychometric properties are established for the PTT, including excellent inter-rater and test-retest reliability.[57] To evaluate the PTT impairment, individual scores were compared to age- and gender-matched cut-off norm-values. PTT values for healthy participants range from 2.50-7.25 mA, determined by age, gender and side of assessment.[84]

Figure 3. Perceptual threshold of touch setup, according to Eek et al.[57]



Proprioceptive somatosensation

The Erasmus MC modification of the (revised) Nottingham sensory assessment (Em-NSA)[83] assesses proprioception by passively moving predefined joints of the upper limb (figure 4). Scores range from 0 (loss of proprioceptive function) to 8 (intact proprioceptive function). A cut-off score of <7 indicates the presence of proprioceptive impairment (movement sense). The Em-NSA has good to excellent intra-rater and inter-rater reliability.[83]

Figure 4. Starting positions and hand grips for testing proprioception with Em-NSA[83]

The thumb finding test (TFT)[85] was used to evaluate proprioception, as it examines the ability to locate the thumb of the affected limb in space. The scoring ranges from 0 to 3 with 0 representing no difficulty; 1 representing a slight difficulty: the patient misses the thumb by less than 15 centimeters and locates the thumb correctly within 5 seconds; 2 representing a moderate difficulty: the patient finds the affected arm and this leads him to the thumb; and 3 representing a severe difficulty: the patient is unable to find the thumb and does not follow the affected arm to locate the thumb. A cut-off score of >0 indicates the presence of impaired proprioception (position sense). Psychometric properties of the TFT are not reported in literature and therefore, we performed a separate reliability study (unpublished data). A total of 43 patients with stroke were assessed within the first six months post stroke and the assessment of the TFT was videotaped. To determine the intra-rater reliability, videos were scored two times, after a minimum of one month in between the scoring. The intra-rater reliability was almost perfect, with a weighted kappa (95% CI) of 0.95 (0.89 to 1.00) and percentage of agreement of 95%.

Higher cortical somatosensation

The Erasmus MC modification of the (revised) Nottingham sensory assessment (Em-NSA)[83] assesses sharp-dull discrimination by alternating sharp (toothpick) and dull (finger) stimuli, at predefined points (figure 2). Scores range from 0 (loss of discriminative function) to 8 (intact discriminative function). A cut-off score of <7 indicates the presence of higher cortical somatosensory impairment. The Em-NSA has good to excellent intra-rater and inter-rater reliability.[83]

During the stereognosis assessment of the original NSA,[86] patients need to identify 11 everyday objects (glass, cup, flannel, sponge, scissors, comb, pencil, biro and three different coins) by touch and manipulation in the affected hand, while blindfolded. Assistance to manipulate the objects in the hand is given by the assessor, when needed. For each object a score from 0 (failed to recognize object) to 2 (recognized object) is given. A cut-off score of <19 indicates the presence of stereognosis impairment. The stereognosis section of the NSA shows a moderate to good test-retest reliability in patients with stroke.[87]

Two-point discrimination (2PD)[88] was assessed at the fingertip of the index finger. Distance between the points was gradually reduced from 15 mm until the patient incorrectly felt only one point. The last correct answer was recorded as the result. The 2PD threshold in healthy controls has a mean of 3.5 mm (±SD 1.7).[68] Subjects with a two-point discrimination threshold higher than 5 mm were classified as having impaired 2PD. Good reliability has been found for the 2PD assessment.[88]

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CHAPTER 1

Functional and motor outcome 5 years after stroke is equivalent to outcome at 2 months: Follow-up of the collaborative evaluation of rehabilitation in stroke across Europe

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Abstract

Background and Purpose: Recovery of patients within the first 6 months after stroke is well documented, but there has been little research on long-term recovery. The aim of this study was to analyse functional and motor recovery between admission to rehabilitation centres and 5 years after stroke.

Methods: This follow-up of the Collaborative Evaluation of Rehabilitation in Stroke Across Europe study, included patients from 4 European rehabilitation centres. Patients were assessed on admission, at 2 and 6 months, and 5 years after stroke, using the Barthel Index, Rivermead Motor Assessment Gross Function, Leg and Trunk function, and Arm function. Linear mixed models were used, corrected for baseline characteristics. To account for the drop-out during follow-up, the analysis is likelihood-based (assumption of missingness at random).

Results: A total of 532 patients were included in this study, of which 238 were followed up at 5 years post stroke. Mean age at stroke onset was 69 (±10 SD) years, 53% were men, 84% had ischemic strokes, and 53% had left-sided motor impairment. Linear mixed model analysis revealed a significant deterioration for all 4 outcomes between 6 months and 5 years (P<0.0001). Scores at 2 months were not statistically significant different from scores at 5 years after stroke. Higher age (P<0.0001) and increasing stroke severity on admission (P<0.0001) negatively affected long-term functional and motor recovery.

Conclusions: Five-year follow-up revealed deterioration in functional and motor outcome, with a return to the level measured at 2 months. Increasing age and increasing stroke severity negatively affected recovery up to 5 years after stroke.

Introduction

Functional disability and motor impairments are important concerns post stroke, therefore improving functional and motor outcome is one of the main goals of stroke rehabilitation.[1] Most recovery is seen in the first weeks after stroke, with the recovery slope reaching a plateau between 3 and 6 months.[2,3] It remains unclear whether early improvements can be sustained long term after stroke. Knowledge of long-term outcomes after stroke rehabilitation is important for the optimization of patient management. Studies on long-term outcome after stroke are few. Most studies are community-based,[4,5] some focus on mortality rates,[6] or others use broad outcome measures, such as being functionally (in)dependent.[7] Long-term functional and motor recovery patterns, measured between admission to rehabilitation and several years after stroke, have received less attention. Two studies with small sample sizes showed a small deterioration between discharge from rehabilitation and several years of follow-up.[8,9] Reutter-Bernays and Rentsch[8] reported a small, nonsignificant decrease in functional outcome over time, whereas Löfgren et al[9] described a significant decrease in overall Fugl-Meyer motor scores between discharge from a geriatric rehabilitation unit and 3-year follow up. Other studies have identified patient characteristics or clinical variables that predicted which individuals were susceptible to deterioration of outcome several years after stroke rehabilitation.[10,11]

Several studies have shown that women have a less favourable outcome after stroke than men.[12,13] Women have more physical impairments and limitations in activities of daily living (ADL) up to 1 year after stroke.[12] A recent systematic review[13] showed that these sex differences persist several years after stroke with women generally having worse functional outcomes, more restrictions in participation, and lower health-related quality of life in the long term after stroke. Furthermore, there is strong evidence that age and stroke severity on admission are significantly associated with functional outcome after 3 months post stroke.[14] Another important factor influencing stroke recovery is stroke pathogenesis. Strokes can be broadly classified as intracerebral haemorrhage (ICH) or cerebral infarction. ICH is associated with a higher risk of death and worse initial functional and motor performance than cerebral infarction, but it is generally alleged that ICH survivors have better neurological and functional recovery than patients having cerebral infarction.[15,16] However, it remains unclear whether the better recovery of ICH patients is sustained in the long-term after stroke.

The aim of this study was to analyse functional and motor recovery in a sample of European stroke rehabilitation patients between admission to rehabilitation centres and 5 years after stroke. In addition, the influence of different patient characteristics on long-term outcome was evaluated. We hypothesize that patients significantly improve in functional and motor performance during the first months after stroke, which will be followed by deterioration in functional and motor outcome during the years of follow-up. Furthermore, we hypothesize that increasing age and stroke severity negatively affect outcome, and that women have a less favourable outcome compared with men. Finally, we hypothesize that patients having an ICH have better functional and motor recovery up until 5 years after stroke than patients having cerebral infarction.

Methods

Study Design, Setting, and Participants

This prospective cohort study is a follow-up of the Collaborative Evaluation of Rehabilitation in Stroke Across Europe (CERISE) project. The project compared stroke care and recovery between 4 European rehabilitation centres[17]: University Hospital, Leuven, Belgium; Nottingham University Hospitals, Nottingham, United Kingdom; RehaClinic, Zurzach, Switzerland; and Fachklinik, Herzogenaurach, Germany. In each centre, inpatient multidisciplinary care was provided in a stroke rehabilitation unit. Patients were recruited using the following inclusion criteria: (1) first-ever stroke as defined by World Health Organization (WHO)[18]; (2) age 40 to 85 years; and (3) scores on Rivermead Motor Assessment[19]: Gross Function (RMA-GF) ≤11, or Leg and Trunk function (RMA-LT) ≤8, or Arm function (RMA-A) ≤12. These cut-off scores were chosen when designing the original CERISE project. Because the aim was to document motor and functional recovery over time, only patients with at least a minimal motor impairment on admission to the rehabilitation centre were included. The exclusion criteria were: (1) other neurological impairments with permanent damage; (2) stroke-like symptoms attributable to subdural hematoma, tumour, encephalitis, or trauma; (3) admission to the centre >6 weeks post stroke; (4) no informed consent; and (5) prestroke Barthel Index (BI)[20] <50. The study was approved by the ethics committee for each centre.

Measurement

A trained assessor in each centre collected all data. The assessors, all qualified as physical therapist or occupational therapist, were trained in the use of the clinical scales. A manual was provided to ensure standardization. For the follow-up study, the same assessors were involved. The project manager (L.D.W.), a trained physical therapist, visited each centre several times both during the data collection of the initial CERISE project and long-term follow-up study. During these visits, several patient assessments were performed together with the assessor in each centre, and feedback was provided. In that way, standardization was ensured. Functional and motor outcome were assessed on admission to the centre, at 2 and 6 months, and at 5 years after stroke with the BI, RMA-GF, RMA-LT, and RMA-A. Functional outcome was assessed using the BI,[20] a scale consisting of 10 items with a score ranging from 0 to 100 (maximum), corresponding to complete independence in basic personal ADL. Adequate reliability and validity of the BI have been reported.[21] The RMA[19] assesses motor performance and consists of 3 sections (RMA-GF, -LT, and -A) in which test items are ordered hierarchically. The items are scored dichotomously (0–1). Maximum scores for each section are 13, 10, and 15, respectively, with a higher score reflecting better motor performance. The RMA has adequate psychometric properties.[22]

On admission to the rehabilitation centre, several variables were documented: age, sex, stroke pathogenesis (ICH or cerebral infarction), side of motor impairment, urinary incontinence, swallowing problems, and severity of stroke (score on the National Institute of Health Stroke scale [NIHSS][23]). In addition, comorbidities were recorded, including history of myocardial infarction, hypertension, atrial fibrillation, coronary heart disease, diabetes mellitus, and hyperlipidaemia.

In this follow-up study, which was conducted between May 2008 and June 2009, patients were contacted at 5 years after stroke. The process of locating patients for the follow-up study was different for all centres, according to the ethics committee requirements. In

Belgium and Switzerland, patients were recontacted by telephone, whereas in Germany and the United Kingdom, patients received a letter. If patients did not answer this letter, death registers were used to determine whether patients were still alive. Patients provided written consent for this follow-up study. Assessments took place at the patients' current residence. Besides RMA-GF, RMA-LT, RMA-A, and BI, also the occurrence of recurrent strokes were documented. This last information was obtained by interviewing the patient and if necessary, relatives or caregivers. Before the start of the long-term follow-up study, a workshop was organized to retrain all researchers in the use of the clinical scales.

Statistical Analysis

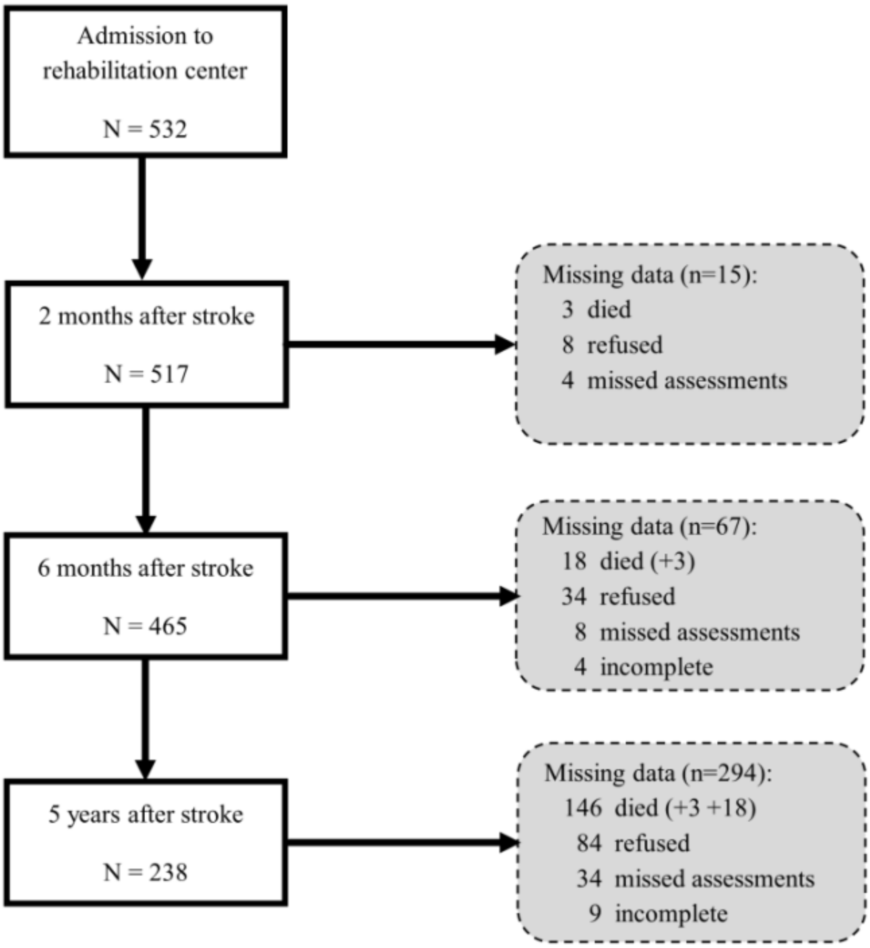
Patients' clinical and demographic characteristics at baseline are presented as frequencies with percentages, means with SD, and medians with interquartile range (IQR), as appropriate. To account for the drop-out during follow-up, the analysis is likelihood-based and therefore valid when the drop-out pattern is at random (missingness at random [MAR]). MAR means that missingness may depend on observed data but, conditional thereupon, not on unobserved data. MAR implies that missingness does not depend on the unobserved value after controlling for other variables in the model or previous observations of the outcome.[24] Therefore, estimates of the recovery patterns are based on data from all patients initially included in the CERISE project. Linear mixed models were used for the estimation of the recovery patterns, with the test score as response variable, and time, outcome measure, and their interaction, evaluated in the explanatory model. Corrections in the model were made for baseline patients' characteristics: age, sex, stroke severity, and stroke pathogenesis. Correlations between repeated measures because of the longitudinal and multivariate aspect were modelled by a fully unstructured residual covariance matrix. In the analysis, time was modelled as a 4-level categorical variable. Patients were assessed on average at 5.62 years post stroke (SD±0.63). To deal with the variability in the time of the long-term follow-up, a continuous variable delta (equal to the deviation of the long-term follow-up time from 5 years) was additionally modelled. Nonlinear trends (quadratic, cubic splines–based trends) for delta were tested using a likelihood ratio test. Consequently, estimates are displayed for exactly 5 years of follow-up. In all models, a random intercept was modelled to account for clustering by centre. Differences in test scores between time points will be tested on both statistical and clinical significance. A change in RMA score per section of <2 points is considered as within the limits of measurement error,[10] corresponding to <13%, 15%, and 20% of the total score of RMA-A, -GF, and -LT, respectively. A change in BI score of <10 points is considered as not reaching the minimal clinical important difference.[25] To evaluate the influence of age, sex, stroke severity, and stroke pathogenesis on the recovery patterns, interaction effects were calculated with the different outcome measures. Recovery patterns are graphically presented for mean age at stroke onset and mean stroke severity on admission. All tests were 2-sided, a 5% significance level was assumed for all tests. Holm (Bonferroni step-down) correction was applied to deal with multiple testing. All analyses were performed using SAS software, version 9.3 of the SAS System for Windows, SAS Institute Inc, Cary, NC.

Results

A total of 532 patients were included in the CERISE study. Figure 1 shows the study flowchart from admission to the rehabilitation centre up to the 5-year follow-up, including details on the drop-out rate. At the time of follow-up, 365 patients were still alive, of whom 238 were willing, and able to participate in the follow-up assessment.

Patients' clinical and demographic characteristics at baseline are shown in Table 1. This is provided for the whole group of patients who were included in the analysis (n=532), for patients assessed at 5-year follow-up (n=238), and for patients alive at 5-year follow-up, but unable or unwilling to participate (n=127). For the patients who entered the analysis, mean age at stroke onset was 69 years (SD, 10) and 53% of the patients were men. A total of 84% of the patients having an ischemic stroke, and the median NIHSS score on admission was 6 of 42 (IQR, 3–10). Initial median BI score was 55 of 100 (IQR, 30–80), median RMA-GF score was 5 of 13 (IQR, 1–9), median RMA-LT score was 6 of 10 (IQR, 2–8), and median RMA-A score was 4 of 15 (IQR, 1–11). Of the 238 patients participating in the long-term follow-up assessment, 32 (13%) suffered a recurrent stroke during follow-up.

Figure 1. **Study flowchart**



Mean change in functional and motor scores of the estimates between the 4 time points are presented in Table 2. There was a 13% to 19% significant increase (P<0.0001) in mean functional and motor scores between admission and 2 months after stroke. Comparing 2 and 6 months after stroke, there was a further improvement (P<0.0001) for all variables, but with a slower rate (6% to 9%) of improvement. Between 6 months and 5 years after stroke, there was a significant decrease of 5% to 10% in mean BI, RMA-GF, RMA-LT, and RMA-A scores (P<0.0001). The change in mean scores of the estimates between 2 months and 5 years after stroke showed no statistical and no clinical difference, as the 95% confidence interval (mean estimate±1.96×SD) of the change scores are all considered measurement error and not exceeding the threshold of minimal clinical important difference.

Table 1. Patients' baseline characteristics

	All patients (n = 532)	Patients assessed at 5-y follow-up (n= 238)	Patients alive at 5-y follow-up, who did not participate (n=127)
Centre, n (%)			
Belgian	127 (23.8)	67 (28.2)	27 (21.2)
British	135 (25.4)	38 (16.0)	48 (37.8)
Swiss	135 (25.4)	78 (32.7)	11 (8.7)
German	135 (25.4)	55 (23.1)	41 (32.3)
Men, n (%)	283 (53.2)	130 (54.6)	62 (48.8)
Age stroke onset, y, mean (±SD)	69.47 (10.28)	67.38 (10.58)	67.13 (10.81)
Stroke pathogenesis, n (%)			
Intracerebral haemorrhage	76 (14.3)	33 (13.9)	25 (19.7)
Cerebral infarction	446 (83.8)	198 (83.2)	101 (79.5)
Not documented	10 (1.9)	7 (2.9)	1 (0.8)
Side of motor impairment, n (%)			
Left	284 (53.4)	121 (50.8)	72 (56.7)
Right	227 (42.7)	108 (45.4)	50 (39.4)
Both	21 (3.9)	9 (3.8)	5 (3.9)
Swallowing problems, n (%)	106 (19.9)	34 (14.3)	25 (19.7)
Urinary Incontinence, n (%)	149 (28)	52 (21.8)	35 (27.6)
Comorbidities, n (%)			
Myocardial infarction	68 (12.8)	24 (10.1)	16 (12.6)
Diabetes mellitus	111 (20.9)	42 (17.6)	22 (17.3)
Hypertension	354 (66.5)	149 (62.6)	87 (68.5)
Atrial fibrillation	104 (19.5)	40 (16.8)	9 (7.1)
Coronary heart disease	135 (25.4)	46 (19.3)	28 (22)
Hyperlipidaemia	219 (41.2)	115 (48.3)	52 (40.9
Number of comorbidities			
None	77 (14.5)	41 (17.2)	20 (15.7)
1 to 2	301 (56.6)	136 (57.1)	80 (63)
3 to 6	154 (28.9)	61 (25.7)	27 (21.3)
NIHSS admission, median (IQR)	6 (3 – 10)	5 (2 – 9)	6 (2 – 10)
BI admission (0-100), median (IQR)	55 (30 – 80)	60 (35 – 85)	55 (30 – 85)
RMA-GF admission (0-13), median (IQR)	5 (1 – 9)	5 (2 – 9)	5 (1 – 9)
RMA-LT admission (0-10), median (IQR)	6 (2 – 8)	6 (3 – 8)	5 (2 – 8)
RMA-A admission (0-15), median (IQR)	4 (1 – 11)	4 (1 – 11)	4 (1 – 11)

BI indicates Barthel Index; IQR, interquartile range; NIHSS, National Institute of Health Stroke Scale; RMA-A, Rivermead Motor Assessment of Arm function; RMA-GF, RMA of Gross Function; and RMA-LT, RMA of Leg and Trunk function.

Table 2. Results of the linear mixed models analysis: Mean (SD) change scores of estimates between time points

Measure score range	Admission- 2 months	Admission- 6 months	Admission- 5 years	2 months- 6 months	2 months- 5 years	6 months- 5 years
BI						
0-100	17.47 (0.86) *	23.58 (1.00) *	16.98 (1.71) *	6.10 (0.69) *	-0.50 (1.58)	-6.60 (1.54) *
Percentage of total score	17.47 (0.86) *	23.58 (1.00) *	16.98 (1.71) *	6.10 (0.69) *	-0.50 (1.58)	-6.60 (1.54) *
RMA-GF						
0-13	2.48 (0.13) *	3.63 (1.15) *	2.66 (0.25) *	1.14 (0.10) *	0.17 (0.23)	-0.97 (0.22) *
Percentage of total score	19.11 (0.97) *	27.89 (1.13) *	20.45 (1.92) *	8.79 (0.78) *	1.34 (1.78)	-7.44 (1.73) *
RMA-LT						
0-10	1.36 (0.10) *	1.98 (0.11) *	1.01 (0.20) *	0.63 (0.08) *	-0.34 (0.18)	-0.97 (0.18) *
Percentage of total score	13.57 (0.98) *	19.82 (1.14) *	10.14 (1.95) *	6.25 (0.78) *	-3.43 (1.81)	-9.68 (1.75) *
RMA-A						
0-15	2.04 (0.15) *	2.94 (0.17) *	2.14 (0.30) *	0.91 (0.12) *	0.10 (0.28)	-0.81 (0.27) †
Percentage of total score	13.56 (1.00) *	19.61 (1.16) *	14.24 (1.99) *	6.06 (0.80) *	0.69 (1.85)	-5.37 (1.79) †

BI indicates Barthel Index; RMA-A, Rivermead Motor Assessment of Arm function; RMA-GF, RMA of Gross Function; and RMA-LT, RMA of Leg and Trunk function. * $p < 0.0001$ (Holm Bonferroni step down correction) † $p < 0.05$

Table 3 shows the influence of age, stroke severity, sex, and type of stroke on functional and motor outcome at the 4 measurement points: admission, 2 months, 6 months, and 5 years after stroke. First, a statistically significant effect ($P<0.0001$) of age on the BI, RMA-GF, and RMA-LT scores on all 4 time points was shown. For the RMA-A scores, age was only of significant influence on admission ($P=0.002$) and at 5 years post stroke ($P=0.019$). A higher age negatively affected functional and motor score. For example, as the age increases by 1 year, the estimated score on the BI decreases with 0.45 (out of 100) on admission and with 0.87 (out of 100) at 5 years post stroke. Second, a statistically significant influence ($P<0.0001$) of stroke severity on all 4 outcome measures, at all 4 time points was seen. Increasing stroke severity negatively affected functional or motor scores. For example, because the NIHSS score increases by 1 point, the estimated score on the BI is 4.07 (out of 100) lower on admission and 2.97 (out of 100) lower at 5 years post stroke. Third, sex was only significantly ($P=0.016$) associated with RMA-GF on admission, with a positive score reflecting a higher mean score for males compared with females. Finally, type of stroke was significantly related to RMA-A scores on admission ($P=0.015$), 2 months ($P=0.002$), and 6 months ($P=0.001$) post stroke. The negative estimates indicate a higher mean score for patients with ICH compared with cerebral infarction.

Table 3. Effects of age, stroke severity, sex and type of stroke on motor and functional outcome, specified at the 4 time points: admission, 2 months, 6 months and 5 years post stroke

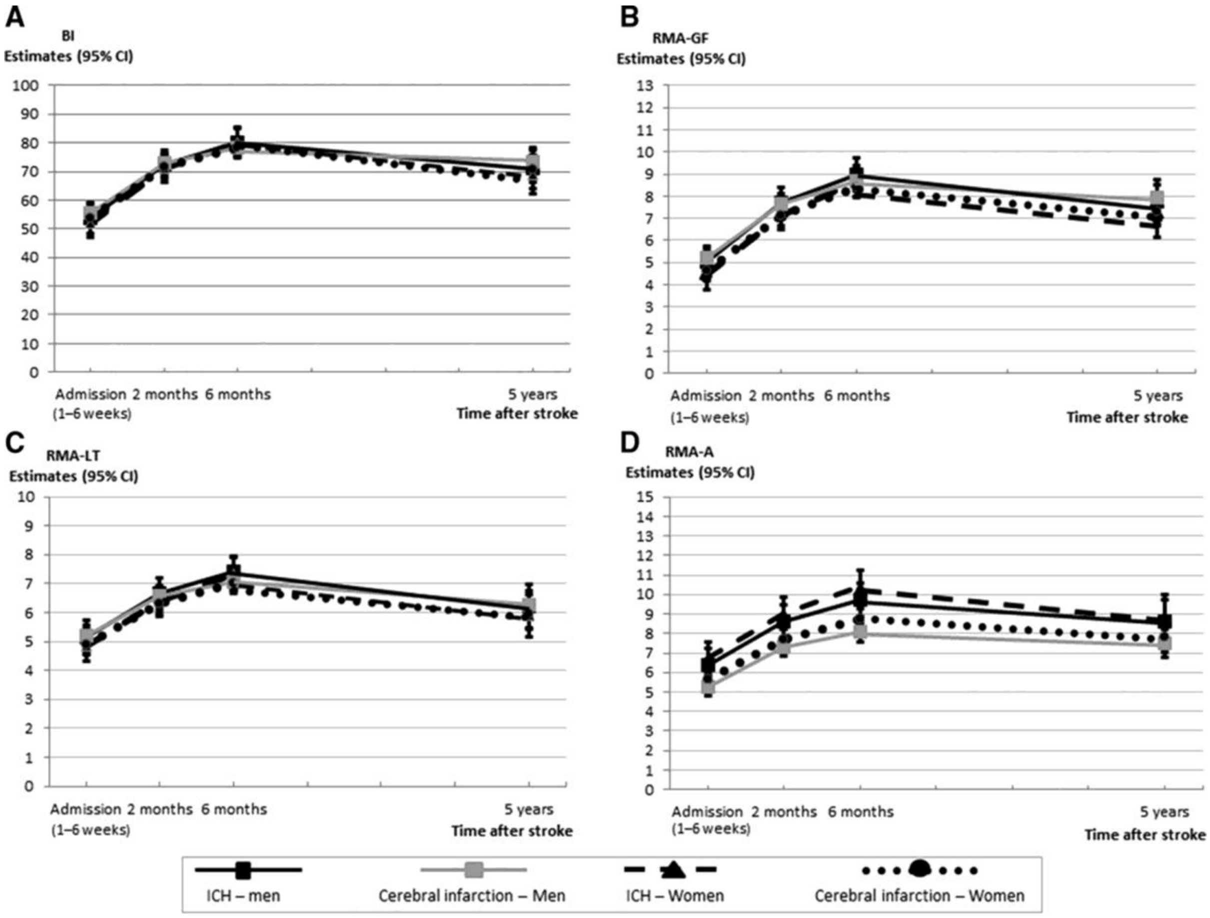
	BI		RMA-GF		RMA-LT		RMA-A	
Effect	Estimate (95% CI)	p	Estimate (95% CI)	p	Estimate (95% CI)	p	Estimate (95% CI)	p
Age: Admission	-0.45 (-0.62;-0.28)	<.0001	-0.05 (-0.07;-0.03)	<0.0001	-0.03 (-0.05;-0.01)	0.0020	0.05 (0.02;0.08)	0.0024
Age: 2 months	-0.62 (-0.78;-0.45)	<.0001	-0.08 (-0.11;-0.06)	<0.0001	-0.05 (-0.07;-0.03)	<.0001	0.01 (-0.02;0.04)	0.5763
Age: 6 months	-0.70 (-0.87;-0.53)	<.0001	-0.10 (-0.12;-0.07)	<0.0001	-0.07 (-0.09;-0.05)	<.0001	-0.01 (-0.04;0.02)	0.5812
Age: 5 year	-0.87 (-1.12;-0.61)	<.0001	-0,13 (-0.16;-0.09)	<0.0001	-0.08 (-0.12;-0.05)	<.0001	-0.05 (-0.09;-0.01)	0.0190
Stroke severity: Admission	-4.07 (-4.38;-3.75)	<.0001	-0.45 (-0.50;-0.40)	<0.0001	-0.43 (-0.47;-0.39)	<.0001	-0.67 (-0.73;-0.61)	<.0001
Stroke severity: 2 months	-3.95 (-4.26;-3.64)	<.0001	-0.52 (-0.57;-0.48)	<0.0001	-0.45 (-0.49;-0.42)	<.0001	-0.80 (-0.86;-0.74)	<.0001
Stroke severity: 6 months	-3.35 (-3.68;-3.01)	<.0001	-0.47 (-0.51;-0.42)	<0.0001	-0.42 (-0.46;-0.38)	<.0001	-0.80 (-0.86;-0.73)	<.0001
Stroke severity: 5 year	-2.97 (-3.52;-2.43)	<.0001	-0.37 (-0.45;-0.29)	<0.0001	-0.37 (-0.43;-0.30)	<.0001	-0.73 (-0.82;-0.64)	<.0001
Gender: Admission	1.42 (-2.02;4.86)	0.4190	0.62 (0.12;1.12)	0.0157	0.33 (-0.05;0.71)	0.0902	0.00 (-0.62;0.62)	0.9892
Gender: 2 months	0.23 (-3.12;3.58)	0.8934	0.39 (-0.12;0.90)	0.1353	0.18 (-0.23;0.58)	0.3975	-0.23 (-0.88;0.42)	0.4925
Gender: 6 months	-1.81 (-5.40;1.78)	0.3239	0.00 (-0.52;0.52)	0.9948	-0.11 (-0.54;0.33)	0.6311	-0.45 (-1.14;0.24)	0.2001
Gender: 5 year	1.87 (-3.49;7.22)	0.4938	0.28 (-0.47;1.04)	0.4587	-0.02 (-0.66;0.63)	0.9572	-0.40 (-1.30;0.49)	0.3765
Type of stroke: Admission	2.56 (-2.25;7.37)	0.2969	0.40 (-0.30;1.10)	0.2613	0.10 (-0.44;0.63)	0.7262	-1.07 (-1.94;-0.21)	0.0151
Type of stroke: 2 months	1.19 (-3.47;5.85)	0.6171	0.19 (-0.52;0.90)	0.5994	0.14 (-0.43;0.70)	0.6397	-1.48 (-2.38;-0.57)	0.0015
Type of stroke: 6 months	-0.62 (-5.62;4.38)	0.8082	-0.44 (-1.16;0.29)	0.2358	-0.16 (-0.77;0.45)	0.6045	-1.82 (-2.78;-0.86)	0.0002
Type of stroke: 5 year	1.67 (-5.78;9.13)	0.6596	0.05 (-1.00;1.09)	0.9282	-0.19 (-1.10;0.73)	0.6888	-0.80 (-2.06;0.46)	0.2110

Age: a positive (negative) estimate indicates an increased (decreased) score with increasing age. Stroke severity: a positive (negative) estimate indicates an increased (decreased) score with increasing severity. Sex: a positive (negative) estimate indicates a higher mean score for men (women). Type of stroke: a positive (negative) estimate indicates a higher mean score for cerebral infarction (intracerebral haemorrhage). BI indicates Barthel Index; CI, confidence interval; RMA-A, Rivermead Motor Assessment of Arm function; RMA-GF, RMA of Gross Function; and RMA-LT, RMA of Leg and Trunk function.

Figure 2 shows the estimates of recovery patterns of the outcome measures, graphically presented for mean age at stroke onset and mean stroke severity on admission. Similar patterns were found for both motor and functional recovery.

Figure 2. **Recovery patterns from admission to the rehabilitation centre up to 5 years after stroke of**

(**A**) the Barthel Index (BI),
(**B**) Rivermead Motor Assessment of Gross Function (RMA-GF),
(**C**) RMA of Leg and Trunk function (RMA-LT), and
(**D**) RMA of Arm function (RMA-A)



ICH indicates intracerebral haemorrhage

Characteristics of the patients assessed at 5-year follow-up are provided in Appendix A. At 5 year post stroke, 33% of the patients had depression and 29% had anxiety disorders. Twenty percent of the caregivers indicated that the care of the patient was a global burden. Eighty percent of the patients visited their general practitioner occasionally during the last year in relation to their stroke, whereas only 4% of the patients did this on a weekly basis. A total of 29% of the patients visited the physical therapist weekly and 8% only occasionally. Therefore, 63% did not receive any physical therapy over the past year. A total of 83% of the patients were living in a community setting, and 17% was institutionalized. When comparing these characteristics and the level of functional and motor outcome at 5 years between patients living in a community setting and patients being institutionalized, we see that patients being institutionalized have significantly worse functional and motor performance, received more physical and occupational therapy during the last year, and have more often dementia compared with patients living in the community setting (Appendix B).

Discussion

This longitudinal, European multicentre study revealed a significant deterioration in long-term functional and motor outcome between 6 months and 5 years after stroke. Interestingly, this study showed that functional and motor outcome at 5 years was equal to outcome at 2 months after stroke. Increasing age and increasing stroke severity negatively affected outcome, and patients with ICH showed better arm function compared with patients with cerebral infarction during the entire study period.

The most important finding of our study is that the level of functional and motor performance at 5 years post stroke was equivalent to the level measured at 2 months. This study supports the importance of intensive stroke rehabilitation in the first weeks after stroke, by the fact that the level of functional and motor performance at 2 months was similar to the level at 5 years. Although intensive inpatient stroke treatment during the first 2 months is highly recommended, one can question whether it would be desirable to reconsider the content and intensity of the treatment afterwards, yet only small clinically significant changes are to be expected. To further maintain or improve the level of long-term motor and functional performance, different models of intermittent training, such as constraint-induced movement therapy,[26] or home-based self-directed therapy with technology support[27] may be a useful alternative to on-going traditional rehabilitation. This needs to be further addressed in future research, assessing both the clinical effectiveness and economic considerations of novel long-term rehabilitation approaches.

Previous results from the CERISE cohort[28] showed that at 6 months post stroke, >50% of the patients still received physiotherapy and 25% received occupational therapy. This study showed that ≈30% of patients received weekly physiotherapy during the last year of follow-up. In theory, in Belgium, Germany, and Switzerland, access to insurance funded rehabilitation can be continued for many years, both for institutionalized- and community living patients, depending on functional disability level and insurance type. However, with the data we have available, we cannot ascertain that the rehabilitation services patients receive at 5 years post stroke are directly related to their first-ever stroke. Other indications might also be the underlying reason why patients receive therapy. At present, little information is available on the duration, frequency, and content of long-term rehabilitation programs across Europe, as well as on the effectiveness of current models. Future studies are needed to map the content and intensity of the current treatment after inpatient rehabilitation across Europe and to evaluate the effect of novel therapy approaches after 6 months post stroke, both from a clinical and an economical perspective, to optimize long-term outcome after stroke.

Our results about the significant deterioration in long-term outcome are consistent with results from other small long-term follow-up studies, investigating recovery patterns after stroke rehabilitation.[8,9] Reutter-Bernays and Rentsch[8] documented a nonsignificant decline of 11% in mean BI between discharge (median time of hospitalization, 96·5 days) and several years of follow-up. Lofgren et al[9] found a significant decrease of 13% in median score on the Fugl-Meyer motor assessment between discharge from a geriatric rehabilitation unit and 3 years later. No significant changes were found about ADL ability, measured with the Katz ADL index. This discrepancy probably reflects the learning of compensation mechanisms during ADL activities. Furthermore, our long-term results need to be interpreted according to normative data on healthy elderly people because a slight deterioration in performance was also seen in a community-dwelling, elderly sample over a period of several years. Hebert et al[29] found a small, statistically significant functional decline over a 2-year period, more specifically in instrumental ADL, but these small changes were not clinically significant, and their study sample was on average 10 years older than our sample. In addition, in our study, only basic personal ADL activities were reported, in which less natural decline would be expected.

Our study showed that patient characteristics had an important influence on recovery. Age and stroke severity on admission were not only strongly associated with functional outcome within the first months after stroke, as reported in previous literature,[14] but remained equally important predictors of both functional and motor outcome several years after stroke. Furthermore, up to 6 months post stroke, ICH survivors showed better motor recovery of the arm compared with patients with cerebral infarction. Our findings did not confirm previous literature indicating that ICH survivors show better functional recovery compared with patients having cerebral infarction.[15,16] This discrepancy in results might be explained by the instrument used to assess functional outcome. In this study, functional recovery was assessed using the BI, assessing patients' level of dependency in basic activities of daily living. This is distinct from the functional independence measure that was used in previous studies and that assesses both physical and cognitive disability. Finally, our study showed that recovery was similar for both men and women after stroke. This is in contrast to previous findings,[13] suggesting that sex differences may be present at stroke onset, remain over several years after stroke, with women generally having worse functional outcomes. The causes of sex differences in functional outcomes are most often explained by the fact that, compared with men, women are older and have worse prestroke function. In our study, prestroke BI scores were equivalent for both genders, which may explain the similar recovery patterns for both men and women.

Some limitations need to be considered. First, recovery was estimated up to 5 years after stroke. However, the time points between 6 months and 5 years were missing. Therefore, we were not able to describe a full pattern of recovery or to determine where the improvement in outcome ends and deterioration starts. Future studies should shorten the intervals between outcome measurements to reveal the turning points in the recovery pattern. Second, the statistical analysis included all patients who were recruited because our main research question was to examine the long-term recovery patterns. Consequently, estimates were made for patients who died during follow-up. Nevertheless, exploratory statistical analysis performed on complete cases, that is, patients who created data at all time points, led to similar results (not presented in the results). Third, in large cohort studies, small differences may become statistically significant because of the large sample size, but do not necessary reflect clinically significant differences. Fourth, this study is not able to provide information for individual prediction for every patient, as it needs further validation in another cohort to be used as a prediction tool. Next, patients were recruited from 4 European rehabilitation centres. This leads to a homogeneous European stroke population in first world nations. Therefore, generalizability of the study findings to third world countries remains uncertain. Finally, the time of admission to the rehabilitation centre varied between 1 and 6 weeks after stroke onset. Patients admitted to the rehabilitation centre at 6 weeks after stroke may have had a more severe stroke, and may have been in a medically unstable condition, compared with those who were admitted earlier. To overcome this possible bias, we corrected for stroke severity in the linear mixed model analysis. However, the time of admission is important for healthcare providers because many questions arise from patients, relatives, and caregivers about future prognosis. Still, to the best of our knowledge, this is the first large cohort study providing long-term outcome after stroke rehabilitation collected in different European centres. Through the use of a mixed model analysis, we were able to make a good estimation of different aspects of motor and functional recovery of this large cohort of patients with stroke.

Summary

In conclusion, our results show that long-term functional and motor outcome after stroke rehabilitation was equivalent to functional and motor performance at 2 months after stroke. Importantly, new strategies need to be identified to improve long-term outcome. Future research should concentrate on assessing both the clinical effectiveness and economic considerations of novel long-term rehabilitation approaches.

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Appendix A. Patient characteristics at 5 year follow-up (n=238)

	n (%)
Comorbidities (n=237)	
Heart disease	77 (32.5)
Diabetes mellitus	50 (21.1)
Hypertension	163 (68.8)
Hyperlipidaemia	110 (46.4)
Epilepsy	19 (8.0)
Dementia	12 (5.1)
Anxiety disorder (HADS –A ≥8) (n=228)	67 (29.4)
Depressive disorder (HADS –D ≥8) (n=228)	79 (33.2)
Caregiver strain (CSI ≥7) (n=203)	40 (19.7)
Use of services at five years after stroke	
General Practitioner	
No	38 (16.0)
Weekly	10 (4.2)
Monthly/occasionally	190 (79.8)
Physiotherapy	
No	150 (63.0)
Weekly	70 (29.4)
Monthly/occasionally	18 (7.6)
Occupational therapy	
No	209 (87.8)
Weekly	22 (9.2)
Monthly/occasionally	7 (2.9)
Living accommodation at 5 years	
Community setting	198 (83.2)
Institutionalized	40 (16.8)

HADS-A: Anxiety subscale of the Hospital Anxiety and Depression Scale, HADS-D: Depression subscale of the Hospital Anxiety and Depression Scale, CSI: Caregiver Strain Index

Appendix B. Patient characteristics of patients living in the community setting and patients being institutionalized at 5 year follow-up (n=238)

	Patients living in community setting (n=198)	Patients being institutionalized (n=40)	P
Comorbidities (n=237): n (%)			
Heart disease	60 (30.5)	17 (42.5)	0.138*
Diabetes mellitus	40 (20.3)	10 (25.0)	0.507*
Hypertension	138 (70.1)	25 (62.5)	0.347*
Hyperlipidaemia	97 (49.2)	13 (32.5)	0.053*
Epilepsy	15 (7.6)	4 (10.0)	0.612*
Dementia	6 (3.0)	6 (15.0)	0.002*
Anxiety disorder (n=228): n (%)	56 (28.9)	11 (32.4)	0.681*
Depressive disorder (n=228): n (%)	63 (32.5)	16 (47.1)	0.099*
Caregiver strain (n=203): n (%)	32 (18.9)	8 (25.0)	0.539*
Use of services at five years after stroke: n (%)			
General Practitioner			0.000*
No	35 (17.7)	3 (7.5)	
Weekly	3 (1.5)	7 (17.5)	
Monthly/occasionally	160 (80.8)	30 (75.0)	
Physiotherapy			0.016*
No	130 (65.7)	20 (50.0)	
Weekly	51 (25.8)	19 (47.5)	
Monthly/occasionally	17 (8.6)	1 (2.5)	
Occupational therapy			0.021*
No	177 (89.4)	32 (80.0)	
Weekly	14 (7.1)	8 (20.0)	
Monthly/occasionally	7 (3.5)	0	
Barthel index score at 5 years: median (IQR)	95 (75-100)	65 (26.25-80)	<0.001†
RMA-GF score at 5 years: median (IQR)	10 (8-11)	6 (1-10)	<0.001†
RMA-LT score at 5 years: median (IQR)	9 (5-10)	4 (2-7)	<0.001†
RMA-A index score at 5 years: median (IQR)	11 (3.5-14)	4 (1-10)	<0.001†

Anxiety disorder: HADS-A ≥8: Anxiety subscale of the Hospital Anxiety and Depression Scale, Depressive disorder: HADS-D ≥8: Depression subscale of the Hospital Anxiety and Depression Scale, Caregiver strain: CSI ≥7: Caregiver Strain Index, RMA-GF: Rivermead Motor Assessment of Gross Function, RMA-LT: Rivermead Motor Assessment of Leg/Trunk, RMA-A: Rivermead Motor Assessment of Arm, IQR: interquartile range * Pearson chi-square test, † Mann-Whitney U test

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CHAPTER 2

How do somatosensory deficits in the arm and hand relate to upper limb impairment, activity and participation problems after stroke? A systematic review

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Abstract

Background: The association between somatosensory impairments and outcome after stroke remains unclear.

Purpose: The aim of this study was to systematically review the available literature on the relationship between somatosensory impairments in the upper limb and outcome after stroke.

Data Sources: The electronic databases PubMed, CINAHL, EMBASE, Cochrane Library, PsycINFO, and Web of Science were systematically searched from inception until July 2013.

Study Selection: Studies were included if adult patients with stroke (minimum n=10) were examined with reliable and valid measures of somatosensation in the upper limb to investigate the relationship with upper limb impairment, activity, and participation measures. Exclusion criteria included measures of somatosensation involving an overall score for upper and lower limb outcome and articles including only lower limb outcomes.

Data Extraction: Eligibility assessment, data extraction, and quality evaluation were completed by 2 independent reviewers. A cut-off score of ≥65% of the maximal quality score was used for further inclusion in this review.

Data Synthesis: Six articles met all inclusion criteria. Two-point discrimination was shown to be predictive for upper limb dexterity, and somatosensory evoked potentials were shown to have predictive value in upper limb motor recovery. Proprioception was significantly correlated with perceived level of physical activity and social isolation and had some predictive value in functional movements of the upper limb. Finally, the combination of light touch and proprioception impairment was shown to be significantly related to upper limb motor recovery as well as handicap situations during activities of daily living.

Limitations: Heterogeneity of the included studies warrants caution when interpreting results.

Conclusions: Large variation in results was found due to heterogeneity of the studies. However, somatosensory deficits were shown to have an important role in upper limb motor and functional performance after stroke.

Introduction

Stroke is a major health burden and the leading cause of serious long-term disability around the world.[1,2] One of the most cumbersome deficits after unilateral stroke is impairment in the contralateral upper limb, typically seen in approximately 70% of the stroke population.[3,4] Despite studies reporting on motor and functional recovery of the upper limb,[5,6] information on the contribution of somatosensory deficits toward motor and functional outcome is scant.

The term somatosensation refers to a sensation arising from the skin, muscles, or joints. Somatosensation is distinct from interoceptive or visceral sensation and special senses such as sight, hearing, smell, and taste. Within the somatosensory system, different modalities such as light touch, proprioception, and stereognosis are identified.[7] Somatosensory deficits of these modalities appear to be common after stroke, with prevalence rates ranging from 11% to 85%.[8] Variability is thought to be related to differences in definition, somatosensory modalities tested, and assessment method used.[8] Most health care professionals consider somatosensory testing an essential part of the clinical assessment process and a valuable method of obtaining information for diagnosis and prognosis of functional ability.[9] Somatosensory impairment also is often a concern of the patient, emphasizing the need to accurately monitor somatosensory impairments with reliable assessment methods to gain further insight into the extent of these deficits after stroke.

An extensive body of animal literature suggests that the projection from the somatosensory cortex to the motor cortex is important in the acquisition of new motor skills.[10,11] Activation of the sensory cortex has been linked to excitation of the motor human cortex as well.[12] The work of Vidoni and Boyd[13] showed that stroke-related somatosensory deficits are associated with disrupted motor learning. They demonstrated that proprioceptive integrity was strongly related to the magnitude of behavioural change associated with learning a repeated tracking task. Furthermore, repetitive peripheral nerve sensory stimulation has been shown to facilitate motor performance.[14]

Several studies investigated the impact of somatosensory deficits on outcome after stroke. Impaired somatosensory function has been related to a longer hospital length of stay and dependency in activities of daily living (ADLs).[15,16] Previous studies[17,18] showed that patients with well-preserved somatosensation achieve a greater improvement in upper limb motor function and are more likely to reach independence in self-care function compared with patients with somatosensory deficiencies. Also, in 2 systematic reviews,[19,20] some of the included studies suggested somatosensory loss to contribute as an independent predictor of upper limb motor and functional recovery. However, these reviews were conducted to summarize potential predictors of upper limb recovery after stroke. Therefore, the focus of these reviews was not on the predictive value of somatosensory impairments, as the clinical somatosensory variables were studied only as co-factors. Also, only longitudinal recovery studies were included in these reviews, and the psychometric properties of the predictor variables and outcome measures were not considered. So far, there is a range of diverse studies with different study designs, all using different measures of somatosensation, both clinical and neurophysiological measures, to determine the impact on various outcome measures after stroke. This variability makes it difficult to draw rigorous conclusions. There is need for a better understanding of the role of different modalities of somatosensation in outcome after stroke.

To our knowledge, there has been no systematic overview of the association between somatosensory impairments in the upper limb and outcome after stroke. This information would be useful to identify appropriate interventions because treatment of somatosensory impairment may positively influence motor output.[8] Therefore, the aim of this study was to systematically review the current, available literature regarding the association of somatosensory impairments in the upper limb with outcome after stroke.

Methods

Data Sources and Searches

We carried out a systematic review on the association between somatosensory impairments in the arm and hand and upper limb impairment, activity, and participation measures after stroke. Guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement for reporting systematic reviews[21] were followed. Articles were identified by searching the following electronic databases: PubMed (from 1966 to July 2013), CINAHL (from 1982 to July 2013), EMBASE (from 1980 to July 2013), Cochrane Library (from 1993 to July 2013), PsycINFO (from 1806 to July 2013), and Web of Science (from 1955 to July 2013). The search strategy was built following consultation with an experienced librarian. Key words for the search strategy relating to the terms stroke, upper extremity, sensation, prognosis, correlation, and prediction, as well as their synonyms and plurals, were included. Appendix A shows the search strategy used for EMBASE, which was adapted for the other electronic databases. In addition, reference lists from the included articles were hand searched to detect further relevant articles.

Study Selection

The inclusion and exclusion criteria for article selection were as follows. Adult participants with a diagnosis of stroke were considered. We included patients with both haemorrhagic and ischemic stroke. Articles were selected for inclusion if the study included at least 10 participants, as determination of clinical prediction rules requires a minimum of 10 participants per prognostic variable investigated.[22] As proposed by Connell and Tyson,[23] independent variables of interest were reliable and valid clinical measures of somatosensory function in the upper limb, such as measures of touch, position sense, stereognosis, and so on. Studies using neurophysiological measures of somatosensation (ie, somatosensory evoked potentials [SSEPs]) also were included. Following the International Classification of Functioning, Disability and Health (ICF) model,[24] outcomes of primary interest comprised standardized measures of impairment, activity, and participation of the upper limb. Only those studies with a correlational analysis or integration of the measure of somatosensation in a predictive regression model were included. Articles needed to be written in English, Dutch, Finnish, or Swedish. We excluded articles that had mixed aetiology groups if data for participants with stroke could not be extracted. Studies using measures of somatosensation involving an overall score for both upper limb and lower limb outcome, as well as those including only lower limb outcome measures, also were excluded.

Data Extraction and Quality Assessment

After removal of duplicates, eligibility assessment was performed by 2 independent reviewers (S.M. and A.H.K.) by screening titles and abstracts. This assessment was subsequently followed by the assessment of the full text of articles. In case of disagreement, consensus was reached through discussion. A specifically developed data extraction sheet was used during the full-text screening. Information was collected about study design (cross-sectional or longitudinal), study setting, time points of follow-up assessments, participant details, inclusion and exclusion criteria, independent variables, outcome variables, statistical analysis, and results on the association between the measure of somatosensation and the outcome. When crucial information was missing, the author of the article was contacted.

The selected studies in the review were subjected to a methodological quality assessment according to the validated Downs and Black quality scale,[25] which was modified to suit the observational study designs of the studies. Due to the lack of a gold standard for assessing quality of observational studies, the Downs and Black quality scale was used, as this scale was recommended in a systematic review[26] of instruments for assessing quality of observational studies (albeit with recognized limitations). Furthermore, the Cochrane Collaboration[27] recommends the same instrument for assessing quality in nonrandomized studies. Therefore, we used the Downs and Black scale. Eight questions of this quality appraisal instrument (questions 4, 8, 14, 15, 19, 23, 24, and 27), therefore, were not applicable due to the nature of the observational study designs included in this review. Additionally, 2 other items (questions 9 and 26) were not applicable for studies with a cross-sectional design. Therefore, when all remaining items were positively appraised, total scores of 20 and 18 points could be assigned to studies with a longitudinal design and a cross-sectional design, respectively. Finally, the total scores were transformed to a percentage. Although no cut-off score is available for the Downs and Black quality scale to identify high-quality studies, a previous study[28] using a similar quality scale showed that studies should have a score of at least 65% of the maximum possible score to be classified as having substantial quality. Therefore, a cut-off score of ≥65% was used for inclusion in this review. Both data extraction and quality evaluation checklists were completed by 2 independent reviewers (S.M. and A.H.K.), and, in case of disagreement, consensus was reached through discussion.

Data Synthesis and Analysis

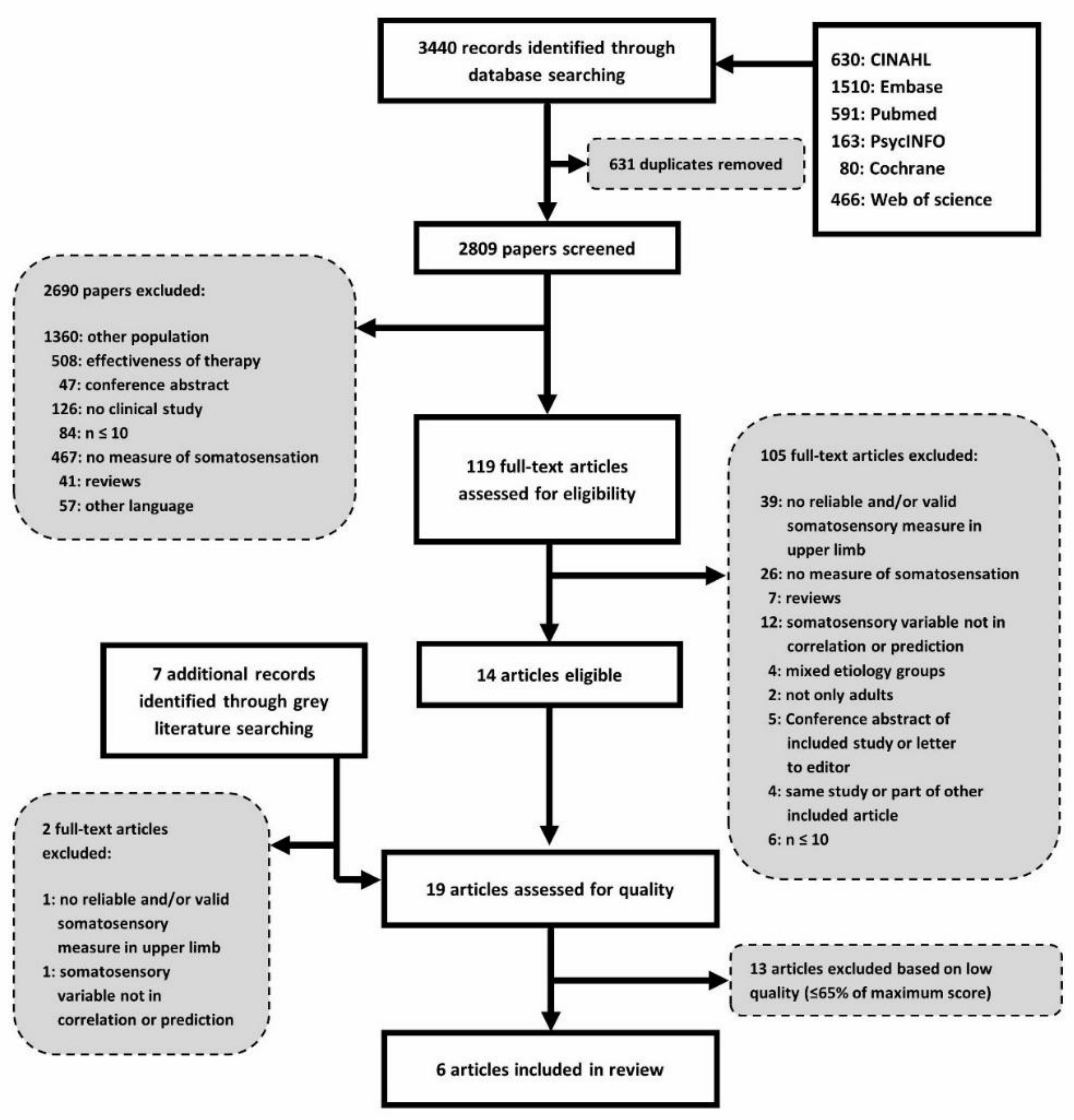
The heterogeneity among studies with regard to the population, somatosensory, and outcome variables used precluded a pooling of results in a formal meta-analysis. Therefore, a descriptive review of the results of the included studies is reported, according to the different outcome measures within the domains of the ICF model.[24] Within each domain, results are presented according to the somatosensory modalities that were measured.

Results

Characteristics of the Included Studies

Our search identified a total of 3,440 hits. A flowchart of the selection process is shown in Figure 1. The process yielded a total of 6 articles[29–34] for inclusion in this systematic review. The main characteristics of the included articles, such as patient characteristics and the somatosensory and outcome measures used, are shown in Appendix B. Five articles[29–31,33,34] had a longitudinal design, and 1 article[32] had a cross-sectional design. Cumulatively, these 6 articles involved 694 adult participants with stroke. The sample size reported within the included articles ranged from 64[31] to 222[34] at baseline, and half of the studies[30,33,34] had an initial sample size of more than 100 participants. Three articles[29,31,33] included patients in the early phase after stroke, ranging from the first week[29] to 1 month[31] after stroke, whereas 1 article[32] focused on patients in the chronic phase (ie, more than 6 months after stroke). With regard to the type of stroke, 58% of the patients were classified with infarction, 6% were classified with hemorrhage, and for 36% of the patients, the pathology was unavailable. In the longitudinal studies reporting loss to follow-up,[29–31,33] the percentage of participants lost to follow-up varied between 12%[33] and 23%.[30]

Figure 1. Flowchart showing how studies were derived



A wide range of somatosensory variables, including neurophysiological and clinical somatosensory measures, was reported on. The search process identified 1 study[31] that measured SSEPs over the trajectory of the median nerve at the wrist. Furthermore, the Fugl-Meyer sensory assessment of the upper limb, assessing light touch and proprioception, was used in 3 studies.[30,33,34] This valid and reliable test is used extensively in stroke studies.[35] Investigating light touch by using Semmes-Weinstein monofilaments was described in 1 study.[29] Intra-class correlation coefficients greater than .90 were reported for both inter-rater and intra-rater reliability.[29] Two-point discrimination[29] and the revised Nottingham Sensory Assessment (NSA)[32] were similarly only tested occasionally, both being reliable assessment methods[29,36] for somatosensory functioning. None of the studies combined SSEPs and a clinical somatosensory measure to evaluate the prognostic information of both type of measures.

Six different outcome measures were identified in the included studies. Of these, according to the classification proposed by Connell and Tyson,[37] 3 outcome measures assessed upper limb impairments: the Fugl-Meyer motor assessment,[31,33] shoulder pain,[33] and the Action Research Arm Test (ARAT).[29] Only 1 measure of activity limitations was used in the included studies: the Motor Activity Log.[34] Additionally, 2 articles reported outcomes at the participation level.[30,32]

The included studies also used a wide range of follow-up periods, ranging from 1 month after discharge from the rehabilitation center[33] to approximately 2 years after stroke.[34] Most of the studies used fixed time points for measurements, such as 3 months,[29] 6 months,[29,31] or 12 months[31] after stroke. Multiple regression analysis was used in all 6 studies.

Results regarding the association between somatosensory deficits and outcome after stroke and an overview of the methodological quality assessment of the 6 included studies are shown in Table 1.

Table 1. Results of association of somatosensory deficits with outcomes after stroke

Study	D&B Score (%)	Somatosensory Measure (Time Point)	Statistical Analysis	Outcome Measure (Time Point)	Results
Body Function					
Au-Yeung, 2006[29]	80	2PD; monofilaments–light touch (1 wk, 2 wk, 3 wk, 4 wk, 2 mo)	Multiple logistic regression; odds ratios	ARAT ≥35 (3 mo, 6 mo)	3 mo: 2PD 1 wk: OR=0.74[b] 2PD 2 wk: OR=0.75[b] 2PD 3 wk: OR=0.72[b] 2PD 4 wk and 2 mo: not retained in multiple regression model Light touch: not retained in multiple regression model 6 mo: 2PD 1 wk: OR=0.83[b] 2PD 2 wk: OR=0.5[b] 2PD 3 wk: OR=0.74[b] 2PD 4 wk and 2 mo: not retained in multiple regression model Light touch: not retained in multiple regression model
Feys et al, 2000[31]	65	SSEP median nerve: present vs absent (admission rehabilitation)	Multiple regression	FM motor assessment upper limb (2 mo, 6 mo, 12 mo)	2 mo: not retained in multiple regression model 6 mo: R^2=.0838[b] 12 mo: R^2=.0864[b]
Paci et al, 2007[33]	80	FM sensory assessment upper limb–light touch and proprioception (admission rehabilitation)	Multiple regression	FM motor assessment upper limb Shoulder pain (30–40 d later)	FM motor assessment upper limb R^2=.01[b] Shoulder pain not retained in multiple regression model
Activity					
Park et al, 2008[34]	80	FM sensory assessment upper limb–light touch and proprioception (3–9 mo)	Univariate logistic regression; multivariate logistic regression	MAL-quality of movement (12 mo later)	Univariate: Light touch: β=–0.538 Proprioception: β=–1.430[b] Multivariate: Proprioception: OR=0.2 (0.06–0.59)[b]
Participation					
Desrosiers et al, 2002[30]	80	FM sensory assessment upper limb–light touch and proprioception (discharge rehabilitation)	Pearson correlation coefficient; multiple regression	LIFE-H questionnaire (6 mo later)	r=.24[b] Not retained in multiple regression model
Morris et al, 2013[32]	83.3	Revised NSA–tactile sensations, proprioception, stereognosis (6 mo)	Bivariate correlations; multiple linear regression	Health-related QOL: Nottingham Health Profile: energy, sleep, social isolation, pain, emotion, physical mobility (cross-sectional: 6 mo)	NHP total: Proprioception: r=−.20 Stereognosis: r=−.09 Tactile sensation: r=−.11 NHP social isolation: Proprioception: r=−.17[b] Stereognosis: r=−.16 Tactile sensation: r=−.18 NHP physical activity: Proprioception: r=−.25[b] Stereognosis: r=.02 Tactile sensation: r=−.03 Not retained in multiple regression model Other subscales NHP: nonsignificant correlations

DB: Downs and Black scale, 2PD: 2-point discrimination, SSEP: somatosensory evoked potentials, ARAT: Action Research Arm Test, FM: Fugl-Meyer, OR: odds ratio, NSA: Nottingham Sensory Assessment, MAL: Motor Activity Log, LIFE-H: Assessment of Life Habits questionnaire, QOL: quality of life, NHP: Nottingham Health Profile, *b* = Significant at P<.05.

Body Function

Light touch and proprioception (Fugl-Meyer sensory assessment)

In the study by Paci et al,[33] a very small proportion of the variance in motor performance in the upper limb 1 month after admission to the rehabilitation centre could be explained by the ability to feel light touch and proprioception in the upper limb (measured on admission to the rehabilitation centre [R^2=.01]). The somatosensory variable was not retained as a predictive factor for shoulder pain at follow-up.

Somatosensory evoked potentials

In the study by Feys et al,[31] SSEPs, measured on admission to the rehabilitation centre, were shown to have predictive value in upper limb motor outcome at 6 and 12 months after stroke. The somatosensory impairment accounted for 8% in the explained variance of upper limb motor outcome.

Two-point discrimination

Au-Yeung[29] found significant odds ratios of 0.51 to 0.83 for the relationship between 2-point discrimination, measured at the first 3 weeks after stroke and an outcome of more than 35 points on the ARAT at 3 and 6 months after stroke. This finding indicates that patients who are able to discriminate between 2 points at the distal pulp of their index finger in the acute phase after stroke have a greater chance of achieving dexterity at 3 and 6 months after stroke.

Pressure perception

The level of pressure perception, as measured with monofilaments, was not retained as a predictive factor for recovery of dexterity in the study by Au-Yeung.[29]

Activity

Light touch and proprioception (Fugl-Meyer sensory assessment)

In the study by Park et al,[34] a significant odds ratio of 0.2 for the relationship between proprioception measured with the Fugl-Meyer sensory assessment at 3 to 9 months after stroke and the quality of movement subscale of the Motor Activity Log 12 months later was demonstrated. A statistically nonsignificant relationship was found for the light touch subscale of the Fugl-Meyer sensory assessment.

Participation

Light touch and proprioception (Fugl-Meyer sensory assessment)

Desrosiers et al[30] found a low but significant univariate correlation (r=.24) between the Fugl-Meyer sensory assessment assessing light touch and proprioception at discharge from the rehabilitation centre and the handicap situations during ADLs and social roles, as assessed with the Assessment of Life Habits questionnaire 6 months later.

Tactile sensation, proprioception, and stereognosis (revised Nottingham Sensory Assessment)

In a cross-sectional study in the chronic phase after stroke by Morris et al,[32] a low but significant negative correlation (r=−.17, r=−.25) was only found between proprioceptive dysfunction and the perceived physical activity subscale and social isolation subscale of the Nottingham Health Profile. The somatosensory variable could not be retained in the multiple regression analysis.

Discussion

It was the aim of this study to systematically review and summarize the current, available literature regarding the association of somatosensory impairments in the upper limb with outcome after stroke. We identified a total of 6 high-quality studies that reported on the influence of somatosensory impairments in the upper limb on impairments in body function, activity, and participation after stroke. These studies showed that 2-point discrimination is a good predictor for upper limb dexterity and that SSEPs have predictive value in upper limb motor recovery. Additionally, proprioception was shown to be significantly correlated with the perceived level of physical activity and social isolation and had some predictive value for the quality of functional movements in the upper limb. Finally, the combination of light touch and proprioception impairment was shown to be significantly related to both upper limb motor recovery and handicap situations during ADLs and social roles. In 4 out of 6 studies, the somatosensory variable could be retained as independent predictor, but with rather low scores in explained variances.

Coupar et al[19] systematically reviewed the literature on potential predictors of upper limb motor and functional recovery after stroke. The authors also found evidence for the association between the presence of SSEPs and better upper limb recovery, but they found inconclusive evidence for an association between clinical somatosensory deficits and upper limb function. It is important to notice that our systematic review had a different emphasis. We included both cross-sectional and longitudinal studies to explore only the association of somatosensory deficits with different outcomes after stroke. Furthermore, we included only reliable and valid measures of somatosensation. This approach resulted in a clear difference in the number of studies included in both reviews. Coupar and colleagues[19] included 19 studies addressing somatosensory deficits after stroke. Our review included only 4 of these studies because of our methodologically rigorous inclusion and exclusion criteria. Additionally, we identified another 2 high-quality studies[30,32] in order to give a more focused and comprehensive review on this topic.

Critical Considerations

Some limitations regarding the studies included in our review need to be addressed. First, it is important to note that almost 40% of the full-text articles we screened for eligibility were excluded based on the absence of psychometric data of the clinical somatosensory measure in the upper limb. This finding revealed the large number of nonstandardized measures of somatosensation used for research purposes, but probably also in the clinical setting. Unfortunately, all efforts invested when conducting these studies are nullified when assessments of unknown psychometric quality are used. Given these findings, it is remarkable that the Nottingham Sensory Assessment was used in only 1 of the included studies, although it was the recommended somatosensory outcome measure in a systematic review by Connell and Tyson[23] regarding outcome measures of somatosensation in neurological conditions. Furthermore, more objective somatosensory measures may have an additional predictive value. A relatively new, promising somatosensory measure is the perceptual threshold of touch,[38] in which high-frequency transcutaneous electrical nerve stimulation is used to activate cutaneous receptors of light touch and their Aβ-fibres in order to determine the threshold of touch in an objective way. Further research is needed to determine the usefulness in clinical practice of this new technique and the predictive value on outcome after stroke. Additionally, robotic devices may help to detect proprioceptive disorders in a more standardized way. Arm position matching tasks with both arms positioned on an exoskeleton robotic device allow different variables to be tracked more accurately and provide reliable 2- or 3-dimensional quantifications of deficits in position sense.[39]

Second, we noted a low proportion of participants included in the studies with an initial diagnosis of somatosensory impairments or only mild somatosensory deficits that were present in studies examining a cohort of people after stroke. Of particular interest is the contribution of somatosensory impairments in motor and functional outcomes in a study sample in which a large proportion of patients are encompassed with somatosensory impairments or patients experience more severe somatosensory impairment. These considerations could lead to different results regarding the contribution of somatosensory impairments in the explained variances of the outcome variable. Furthermore, none of the studies explored the lesion location and volume of the stroke. This would seem to be an important factor affecting somatosensation. In 3 of the 6 included studies, magnetic resonance imaging findings were studied as 1 of the other independent variables in the regression models. Only 1 study (Au-Yeung[29]) demonstrated a significant correlation with outcome after stroke. None of the studies investigated the relationship between the location and extent of the lesion with somatosensory impairments.

Finally, we need to consider the methodological quality of the studies. Thirteen out of 19 studies eligible for inclusion had only poor to moderate quality (score <65% of the maximum score) and, therefore, were excluded from this review. This finding indicates that most of the studies (68%) in this research field are of insufficient rigor to allow meaningful conclusions; therefore, results need to be interpreted with caution. Although we acknowledge the difficult nature of carrying out this kind of study, new large, high-quality cohort studies will be needed in the future.

An important consideration of our review relates to the heterogeneity of the included studies, which warrants caution when interpreting our results. Many different study designs, somatosensory variables, and outcome measures were used, and there was great variability in lengths of follow-up, data analysis, and presentation methods. Five of the included studies had a longitudinal design, which is crucial to assess the impact of somatosensory problems on recovery after stroke. However, based on previous literature, high-quality cross-sectional studies also may provide valuable information. The cross-sectional study included in this review allows us to gain insights into the time-independent relationship between somatosensation and health-related quality of life at 6 months after stroke.

The heterogeneity of the included studies also prevented us from pooling data and drawing more detailed conclusions about the impact of different somatosensory modalities, such as light touch or proprioception, on upper limb motor and functional outcome after stroke. Bias in setting and study participants needs consideration when indirectly comparing results across studies. Furthermore, the question of whether neurophysiological measures have a higher predictive value compared with clinical somatosensory measures in outcome after stroke could not be answered due to the small number of high-quality studies using neurophysiological measures of somatosensation and the lack of studies combining both neurophysiological and clinical somatosensory measures in predicting motor outcome after stroke. Moreover, we expected to find stronger correlations in cross-sectional studies than in longitudinal studies. Conversely, we could not find any differences in results between cross-sectional and longitudinal studies, possibly due to the high heterogeneity of the included studies and the small amount of high-quality cross-sectional studies. Another drawback is publication bias. Studies with significant results are more likely to be published. We addressed this limitation through a rigorous searching process in different databases. It is reassuring that our search identified studies similar to those in other recent reviews in this area.

Finally, it should be noted that the quality assessment criteria are also a concern with this type of review. Because of the lack of a gold standard for assessing quality of observational studies, we modified the methodological quality assessment of the Downs and Black quality scale.[25] This scale originally was designed to assess the methodological quality both of randomized and nonrandomized studies of health care interventions. Different questions of this quality appraisal instrument were not applicable due to the nature of the observational study designs included in this review. Through omitting 2 additional questions in the quality appraisal of cross-sectional studies, we can guarantee that the quality assessment was not biased toward longitudinal studies and that there was no penalization of studies with a cross-sectional design. Important to note is the fact that some of the articles included for quality appraisal were published long before the concepts brought forward in the article by Downs and Black were ever published. This may be 1 factor explaining the low scores in the quality rating.

Implications for Practice

Recommendation for practice includes the use of reliable and valid measurement instruments. The importance of somatosensory testing as an essential part of the clinical assessment process is recognized by both patients and health care personnel,[9] emphasizing the need for accurate, reliable assessment methods. As pointed out above, a huge dropout of studies was attributed to the unpublished psychometric properties of the included measures of somatosensation. The recent publication proposed by Connell and Tyson[23] offers a guideline for using reliable, valid, and clinically useful measures of somatosensation. Although the measurement of all somatosensory modalities looks impracticable and difficult to justify in the clinical setting in patients with stroke, we do recommend 1 testing of each modality of somatosensation, such as light touch, pressure, pinprick, proprioception, discrimination tasks, and stereognosis. Furthermore, it is important to assess patients from the acute phase after stroke along the rehabilitation process to accurately monitor progress. Also, up to now, results from somatosensory assessments have not been routinely used to set goals for treatment programs. Treatment of somatosensory deficits is needed because it also may positively influence motor output.[8]

A recent systematic review conducted by Doyle et al[7] examined interventions for somatosensory impairment in the upper limb after stroke and indicated insufficient evidence about the effects of treatment interventions. This finding was attributed to the large variety of interventions and the small number of included articles. Still, some of the studies included in the review of Doyle et al suggested preliminary evidence for the effects of some specific interventions, such as thermal stimulation and intermittent pneumatic compression for improving somatosensation after stroke. Another recent randomized controlled trial[40] provided evidence for improvement in functional sensory discrimination capacity after stroke when providing patients intensive sensory discrimination training based on perceptual learning for a total of 10 hours. These findings provide support for introducing interventions for somatosensory impairment in rehabilitation programs for patients with stroke.

Implications for Research

This review has highlighted the need to use reliable and valid measures of somatosensory functions in research. Additionally, more standardized somatosensory measures, such as the perceptual threshold of touch,[38] need to be investigated to determine the predictive value on outcome after stroke. Furthermore, important gaps in the current knowledge need to be addressed. First, this review showed a large range in strength of the relationship between somatosensory and motor or functional outcome after stroke. Larger, high-quality cohort studies combining neurophysiological and clinical somatosensory measures of different modalities are needed to determine this relationship with more accuracy. Second, the relationship between the lesion location and extent of the stroke with somatosensory impairments needs to be further explored, as this information will increase our insights into the neural correlates of somatosensory processing. Third, the quality assessment of observational studies needs to be standardized, and validity needs to be established. Finally, insights are lacking regarding the extent of deficits in different somatosensory modalities and the recovery patterns of the different somatosensory modalities after stroke. These insights are crucial in guiding and delineating treatment interventions for somatosensory deficits in patients with stroke.

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Appendix A. Search strategy used for EMBASE and adapted for the other databases

Searches		Results
1.	exp cohort analysis/	117266
2.	incidence.sh.	163175
3.	exp mortality/	402196
4.	follow up/	518734
5.	prognos$.tw.	300513
6.	predict$.tw.	759488
7.	course$.tw.	317689
8.	predictor$.tw.	194676
9.	exp statistical model/	83263
10.	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9	2149121
11.	exp cerebrovascular disease/	278019
12.	exp basal ganglion/	63154
13.	exp brain ischemia/	64190
14.	exp carotid artery disease/	28970
15.	exp cerebrovascular accident/	35741
16.	exp brain infarction/	33297
17.	exp brain ischemia/	64190
18.	intracranial hypertension/ or intracranial aneurysm/ or intracranial pressure/ or intracranial hypotension/	22270
19.	exp brain hemorrhage/	50388
20.	exp brain embolism/	3845
21.	exp brain arteriovenous malformation/	3887
22.	exp brain vasospasm/	3683
23.	artery dissection/	4643
24.	Stroke.tw.	132327
25.	poststroke.tw.	2446
26.	post-stroke.tw.	4267
27.	cerebrovasc$.tw.	28724
28.	brain vasc$.tw.	652
29.	cerebral vasc$.tw.	4308
30.	cva$.tw.	2818
31.	apoplex$.tw.	1153
32.	SAH.tw.	6179
33.	exp hemiplegia/	6373
34.	exp paresis/	3898
35.	hemipleg$.tw.	5736
36.	hemipar$.tw.	7980
37.	paresis.tw.	5451
38.	paretic.tw.	1526
39.	11 or 12 or 13 or 14 or 15 or 16 or 17 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38	389644

Searches		Results
40.	10 AND 39	108798
41.	exp arm/	76240
42.	(upper adj3 (limb$ or extremity)).tw.	23134
43.	arm.tw.	74444
44.	shoulder.tw.	29863
45.	elbow.tw.	15038
46.	forearm.tw.	19668
47.	hand.tw.	196447
48.	wrist.tw.	16971
49.	finger.tw.	35216
50.	fingers.tw.	12217
51.	41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50	381951
52.	40 AND 51	4262
53.	exp sensation/	10789
54.	sensory dysfunction/	9078
55.	motor performance/	29998
56.	convalescence/	28267
57.	functional assessment/	37419
58.	53 or 54 or 55 or 56 or 57	110746
59.	52 AND 58	699

Appendix B. Characteristics of included studies

Study	D&B Score (%)	n	Study Population	First Observation	FU	Statistical Analysis	Somatosensory Measure (Modality)	Other Correlated/ Predictive Factors	Outcome Measure
Au-Yeung, 2006[29]	80	70: 1 wk 57: FU	100% ischemic Acute (<1 wk) Mean age: 69.7 y (SD=10.2) >45 y 65% impaired 2PD, 77% impaired light touch	1 wk	3 mo 6 mo	Multiple logistic regression; odds ratios	Discriminator (2PD)[b] Monofilaments (light touch)	Side lesion, site lesion, stroke severity: NIHSS, spatial neglect, muscle tone upper limb, Motricity Index arm,[b] grip strength hand, pinch grip strength, cognitive status	ARAT ≥35
Desrosiers et al, 2002[30]	80	132: discharge 102: 6 mo after discharge	Type stroke: N/A Subacute–chronic Mean: 110 d (SD=45.5) Mean age: 60.9 y (SD=13.5) >18 y Mild somatosensory deficits	Discharge rehabilitation center	6 mo later	Pearson correlation coefficient; multiple regression	FM sensory assessment upper limb (light touch and proprioception)	FM motor assessment upper and lower limb, FM sensory assessment lower limb, cognitive status, coordination,[b] visual perception, spatial neglect, comorbidities,[b] Berg Balance Scale,[b] TEMPA, depression,[b] perceived social support, walking endurance, walking speed, language, incontinence, time since stroke, length of stay,[b] motivation, age[b]	LIFE-H Questionnaire Assessment of life habits: degree of handicap in ADL or IADL, social roles
Feys et al, 2000[31]	65	64: admission (50 MEP) 61: 2 mo (43 MEP) 58: 6 mo 52: 12 mo	95% ischemic Acute (2–5 wk) Mean age: 63.7 y (SD=11.3), range=38–88 37% absent SSEP	Admission rehabilitation center	2 mo 6 mo 12 mo	Multiple regression	SSEP median nerve (proprioception)[b]	Barthel Index, FM motor assessment upper limb,[b] muscle tone,[b] MEP parameters	FM motor assessment upper limb
Morris et al, 2013[32]	83.3	85	89.4% ischemic Chronic (6 mo) Mean age: 67.6 y (SD=11.4) Mild somatosensory deficits	6 mo		Bivariate correlations Multiple linear regression	Revised NSA (tactile sensation, proprioception, stereognosis)	Age, sex, side of stroke, hand dominance, stroke type, days to discharge, ARAT, 9-Hole Peg Test, Rivermead Motor Assessment arm,[b] Barthel Index,[b] Hospital Anxiety and Depression Scale[b]	Nottingham Health Profile: energy, sleep, pain, social isolation, physical mobility, emotion= health-related QOL
Paci et al, 2007[33]	80	121: admission 107: 30–40 d after discharge	Type stroke: N/A Acute (<1 mo) Mean age: 71.6 y (±10 y) Somatosensory deficits: N/A	Admission rehabilitation center	30–40 d later	Multiple regression	FM sensory assessment upper limb (light touch and proprioception)[b]	Age, sex, side of stroke, time since stroke, length of stay FM motor assessment upper limb,[b] shoulder pain,[b] subluxation[b]	FM motor assessment upper limb, shoulder pain
Park et al, 2008[34]	80	222	88% ischemic Chronic (3–9 mo) Mean age: 62.2 y (SD=13) >18 y 43% impaired light touch, 30% impaired proprioception	3–9 mo	12 mo later	Univariate logistic regression; multiple logistic regression	FM sensory assessment upper limb (light touch and proprioception)[b]	Age,[b] sex, side of stroke, type of stroke, concordance, time since stroke, Motor Activity Log,[b] Wolf Motor Function Test,[b] FM motor assessment upper limb, muscle tone, visual perception	Motor Activity Log: quality of movement

D & B score: Downs and Black score, n: sample size, FU: Follow-up assessment, H: hours, D: days, W: week(s), M: months, Y: years, *: independent predictor in multivariate model, SSEP: SomatoSensory Evoked Potentials, 2PD: 2-Point Discrimination, NIHSS: National Institute of Health Stroke Scale, ARAT: Action Research Arm Test, N/A: not available, FM: Fugl-Meyer, ADL: Activities of Daily Living, IADL: Instrumental Activities of Daily Living , LIFE-H: Assessment of Life Habits, TEMPA: Test d'Evaluation de la performance des Membres Supérieurs des Personnes Agées, QOL: Quality Of Life, MEP: Motor Evoked Potentials, NSA: Nottingham Sensory Assessment

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CHAPTER 3

Somatosensory impairments in the upper limb post stroke: distribution and association with motor function and visuo-spatial neglect

Neurorehabilitation and Neural Repair [under review]

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Abstract

Background: A thorough understanding of the presence of different upper limb somatosensory deficits post stroke and the relation with motor performance remains unclear. Additionally, knowledge about the relation between somatosensory deficits and visuo-spatial neglect is limited.

Objective: To investigate the distribution of upper limb somatosensory impairments and the association with uni- and bimanual motor outcome and visuo-spatial neglect.

Methods: A cross-sectional observational study was conducted including 122 patients within 6 months after stroke (median 82 days, IQR 57-133 days). Somatosensory measurement included the Erasmus modified Nottingham sensory assessment (Em-NSA); perceptual threshold of touch (PTT); thumb finding test; two-point discrimination, and stereognosis subscale of the NSA. Upper limb motor assessment comprised the Fugl-Meyer assessment, motricity index, action research arm test and adult-assisting hand assessment stroke. Screening for visuo-spatial neglect was performed using the star cancellation test.

Results: Upper limb somatosensory impairments were common, with prevalence rates ranging from 21-54%. Low to moderate Spearman rho correlations were found between somatosensory and motor deficits (r=.22-r=.61), with the strongest associations for PTT (r=.56-r=.61) and stereognosis (r=.51-r=.60). Visuo-spatial neglect was present in 27 patients (22%). Between-group analysis revealed significantly more often and more severe somatosensory deficits in patients with visuo-spatial neglect ($p<0.05$). Results showed consistently stronger correlations between motor and somatosensory deficits in patients with visuo-spatial neglect (r=.44-r=.78) compared to patients without neglect (r=.08-r=.59).

Conclusions: Somatosensory impairments are common in sub-acute patients post stroke and related to motor outcome. Visuo-spatial neglect was associated with more severe upper limb somatosensory impairments.

Introduction

The somatosensory system allows us to interpret somatosensory stimuli received from receptors located in the joints, ligaments, muscles and skin.[1] Somatosensory information such as pain, pressure or joint position sense, is then processed in different brain centers to modulate incoming sensory information.[1] Key brain regions involved in processing somatosensory information are the primary and secondary somatosensory cortex, the thalamus, insula, posterior parietal cortex and the cerebellum.[2] Within the somatosensory system, a classification in exteroceptive, proprioceptive and higher cortical somatosensation can be identified.[3,4] Each of these categories include a set of somatosensory modalities such as light touch and pain within exteroceptive somatosensation, position and movement sense within proprioceptive somatosensation and somatosensory discrimination sense within higher cortical somatosensation.[3] Deficits of these somatosensory modalities are common after stroke, with prevalence rates ranging from 11% to 85%.[5-7] Variability is attributed to differences in definition, study populations, somatosensory modalities tested, and assessment method used.[5] Up to now, most studies concentrated on identifying deficits in a single somatosensory modality such as light touch perception or joint position sense. Therefore, a thorough understanding of the prevalence and distribution of deficits in different exteroceptive, proprioceptive and higher cortical somatosensory modalities in the sub-acute phase post stroke is missing.

Along with upper limb somatosensory impairments, approximately 70% of patients post stroke experience motor impairments in the affected upper limb.[8] Our recent systematic review[9] investigating the impact of somatosensory deficits on outcome after stroke, showed that different somatosensory impairments are negatively associated with motor recovery in the upper limb. Despite these results, the review highlighted the need for large high-quality cohort studies that combine somatosensory measures of different modalities to determine the relationship with both unimanual and bimanual motor performance with more accuracy.

It is well known from previous literature that visuo-spatial neglect, a neuropsychological disorder often encountered post stroke, negatively affects recovery.[10-16] Unilateral visuo-spatial neglect has been defined as the inability to detect, respond to, and orient towards novel and significant stimuli occurring in the hemi space contralateral to a brain lesion.[17] The reported incidence of neglect ranges between 10% and 80%.[18,19] Variability among studies is again believed to be related to subject selection, nature and timing of the assessment and differences in definitions of this complex phenomenon.[20] It was recently shown that the time course of recovery of visuo-spatial neglect mimics the recovery patterns of other neurological impairments such as motor or functional outcome, with large improvements in the first weeks post stroke, and with the recovery reaching a plateau around three months post stroke.[21] Visuo-spatial neglect is known to increase length of hospital stay[11], may hinder response to therapy[11] and is negatively associated with performance in activities of daily living.[12] Nijboer et al.[13] showed that on admission to the rehabilitation centre, patients with visuo-spatial neglect have significantly worse functional performance compared to patients without neglect, as measured with the Barthel index and functional independence measure. A detailed analysis of the different domains of the functional independence measure showed that on average, patients with neglect scored significantly lower on self-care, transfers and locomotion compared to the non-neglect patients, whereas no differences were found between groups for sphincter control and cognition.[13]

Furthermore, visuo-spatial neglect is linked to poor motor performance[13,15,16] and has a suppressive effect on upper limb motor recovery, mainly during the first three months post stroke, when spontaneous neurological recovery is taking place.[14] Despite the shared neuro-anatomy between somatosensory processing and the presence of visuo-spatial neglect in areas of the parietal cortex,[22,23] only a few studies[13,14,24-27] reported the relationship between visuo-spatial neglect and somatosensation in the upper limb. The presence of visuo-spatial neglect seems to be associated with more severely affected limb position sense in the arm,[13,14,25-27] and is predictive for impaired limb movement sense.[24] However, information on the association between visuo-spatial neglect and exteroceptive or higher cortical somatosensory deficits after stroke is lacking.

The primary objectives of this study were therefore (1) to map the prevalence and distribution of different exteroceptive, proprioceptive and higher cortical somatosensory impairments in the upper limb and (2) to study the association between different somatosensory impairments and unimanual and bimanual motor function post stroke. A secondary objective was to investigate whether the presence of neglect is associated with the occurrence and severity of somatosensory impairments, and whether the association between somatosensory impairments and uni- and bimanual motor outcome is different for patients with and without visuo-spatial neglect. The primary hypothesis was that, in line with previous literature,[5-7] upper limb somatosensory deficits are common, with higher cortical somatosensory deficits being the most prevalent due to the fact that for higher cortical sensation such as stereognosis, an intact primary sensation (i.e. touch and pressure) as well as higher cortical discriminative function is required. Secondly, based on our recent systematic review,[9] we hypothesize that somatosensory impairments are moderately associated with uni- and bimanual motor function. Thirdly, based on the closely related neuro-anatomy,[2,22,23] we hypothesize that visuo-spatial neglect is highly associated with the prevalence and severity of exteroceptive, proprioceptive and higher cortical somatosensory deficits. Finally, based on our systematic review[9] we expect that somatosensory deficits are moderately associated with uni- and bimanual motor function, equally in patients with and without visuo-spatial neglect.

Methods

Participants

For this cross-sectional observational study, one hundred twenty-two (n=122) patients were assessed between October 2013 and August 2014 in seven neurorehabilitation units in Belgium (n=102) or in the home environment of the patient (n=20). Patients assessed in the home environment all completed inpatient rehabilitation, and were still enrolled in outpatient physical therapy. The inclusion criteria were: (1) first-ever stroke as defined by the World Health Organization (WHO)[28]; (2) assessed within the first six months after stroke; (3) motor and/or somatosensory impairment in the upper limb, using outcome measures as described below; (4) minimally 18 years old, and; (5) substantial cooperation to perform the assessment. Patients were excluded if they had: (1) a pre-stroke Barthel index[29] score of < 95 out of 100; (2) other neurological impairments with permanent damage such as multiple sclerosis or Parkinson’s disease; (3) a subdural hematoma, tumor, encephalitis or trauma that led to similar symptoms as a stroke, and; (4) serious communication, cognitive or language deficits, which could hamper the assessment. Subjects signed a written informed consent form prior to participation. Ethical approval was obtained from the Ethics Committee of the University Hospital of Leuven, and all participating centers.

Patients were assessed in a single test session. One trained researcher performed the data collection. Patients' baseline characteristics were assessed, including age at stroke onset, gender, comorbidities (cumulative illness rating scale, CIRS[30]), hand dominance, time post stroke, lateralization and type of stroke.

Outcome measures

Somatosensory assessment

<u>Exteroceptive somatosensation</u>

The Erasmus MC modification of the (revised) Nottingham sensory assessment (Em-NSA)[31] assesses light touch, pressure and pinprick. Light touch was applied with a cotton wool, pressure with the index finger and pinprick with a toothpick, at predefined points. Scores for each modality range from 0 (loss of somatosensory function) to 8 (intact somatosensory function). A cut-off score of <7 indicates the presence of somatosensory impairment. The Em-NSA has good to excellent intra-rater and inter-rater reliability.[31]

The perceptual threshold of touch (PTT)[32] is the minimal stimulus level of touch that is detectable. A transcutaneous electric nerve stimulation (TENS) was applied with a portable device: A CEFAR Primo Pro (Cefar Medical AB, Sweden). Round electrodes, with a diameter of 3 cm, were applied to the index finger and bulb of the thumb. A high-frequency constant current of 40Hz with single square pulses of 80µs pulse duration is applied. The amplitude is gradually increased with increments of 0.5mA, until a tingling sensation is being perceived at the index finger. Good psychometric properties are established for the PTT.[32] To evaluate the PTT impairment, individual scores were compared to age- and gender-matched cut-off norm-values.[33]

Proprioceptive somatosensation

The Erasmus MC modification of the (revised) Nottingham sensory assessment (Em-NSA)[31] assesses proprioception by passively moving predefined joints of the upper limb. Scores range from 0 (loss of proprioceptive function) to 8 (intact proprioceptive function). A cut-off score of <7 indicates the presence of proprioceptive impairment (movement sense). The Em-NSA has good to excellent intra-rater and inter-rater reliability.[31]

The thumb finding test (TFT)[34] was used to evaluate proprioception, as it examines the ability to locate the thumb of the affected limb in space. The scoring ranges from 0 (no difficulty) to 3 (severe difficulty). A cut-off score of >0 indicates the presence of impaired proprioception (position sense).

Higher cortical somatosensation

The Erasmus MC modification of the (revised) Nottingham sensory assessment (Em-NSA)[31] assesses sharp-dull discrimination by alternating sharp (toothpick) and dull (finger) stimuli, at predefined points. Scores range from 0 (loss of discriminative function) to 8 (intact discriminative function). A cut-off score of <7 indicates the presence of higher cortical somatosensory impairment. The Em-NSA has good to excellent intra-rater and inter-rater reliability.[31]

During the stereognosis assessment of the original NSA,[35] patients need to identify 11 everyday objects by touch and manipulation in the affected hand, while blindfolded. Assistance to manipulate the objects in the hand is given by the assessor, when needed. For each object a score from 0 (failed to recognize object) to 2 (recognized object) is given. A cut-off score of <19 indicates the presence of stereognosis impairment. The stereognosis section of the NSA shows a moderate to good test-retest reliability in patients with stroke.[36]

Two-point discrimination (2PD)[37] was assessed at the fingertip of the index finger. Distance between the points was gradually reduced from 15 mm until the patient incorrectly felt only one point. The last correct answer was recorded as the result. The 2PD threshold in healthy controls has a mean of 3.5 mm (±SD 1.7).[38] Subjects with a two-point discrimination threshold higher than 5 mm were classified as having impaired 2PD. Good reliability has been found for the 2PD assessment. [37]

In summary, based on the different assessments, exteroceptive somatosensation included the measures of light touch, pressure and pinprick (of the Em-NSA), and the perceptual threshold of touch. Proprioceptive somatosensation was assessed using the thumb finding test and the proprioception subscale of the Em-NSA. Finally, higher cortical somatosensation comprised of sharp-dull discrimination, stereognosis and two-point discrimination.

Assessment of visuo-spatial neglect

The star cancellation test (SCT)[39] from the behavioural inattention test (BIT)[40] was used to assess the presence of visuo-spatial neglect. A previous study[41] found the SCT to be the most sensitive paper-and-pencil measure of visuo-spatial neglect. Different stimuli are presented on a piece of paper, including large stars, letters, short words and small stars. The test page is placed at the patient's midline. The task is to locate and cross out all small stars. A cut-off score of <44 (out of 54 stars) indicates the presence of visuo-spatial neglect.[42] A lateralization index was calculated from the ratio of stars cancelled on the left of the page to the total number of stars cancelled, according to Halligan et al.[43] Laterality scores range from 0 to 1 with values near 0.5 suggesting unbiased performance, between 0 and 0.46 indicating visuo-spatial neglect in the left hemispace and between 0.54 and 1 indicating visuo-spatial neglect in the right hemispace. Interrater reliability of the SCT is found to be high.[44]

Motor assessment

The Fugl-Meyer assessment upper extremity (FMA-UE)[45] is a reliable and valid measure for overall motor impairment, with a total score between zero and 66. The action research arm test (ARAT)[46] measures motor performance in 4 different subscales: grasp, grip, pinch and gross movement, with a maximum score of 57. Reliability[47] and validity[48] are established for the ARAT. The arm section of the motricity index (MI)[49] is a reliable measure of muscle strength during pinch grip, flexion of the elbow and abduction of the shoulder. Total scores vary between 0 and 100. The adult assisting hand assessment stroke (Ad-AHA Stroke), a Rasch-based performance scale, measures how effectively the affected hand is spontaneously used during performance of a bimanual task. Performance of the semistructured present-task was video-recorded. Nineteen test items, describing different object-related hand actions are scored on a 4-point scale rating the quality of performance. The raw scores are then converted through the Rash analysis to logit-scores varying between 1 and 100, with higher scores indicating higher bimanual ability levels (unpublished results).[50]

Statistical analysis

Patients' clinical and demographic characteristics were displayed as frequencies with percentage, mean with standard deviation (SD) and median with interquartile range (IQR). The prevalence and distribution of deficits in different somatosensory modalities such as light touch, position sense or stereognosis, were calculated using frequencies with percentages according to the presence of exteroceptive, propriocepive or higher cortical somatosensory problems. Therefore, the different somatosensory variables were dichotomized according to the presence of a deficit or normal functioning based on the above mentioned predefined cut-off values. Furthermore, associations between somatosensory and motor impairments were assessed using Spearman rank correlation coefficients. For this analysis, the full score range of the somatosensory and motor variables were used. Strength of the relation was interpreted according to Munro's correlation descriptors[51]: very low: r = 0.01-0.24, low: r = 0.25-0.49, moderate: r = 0.50-0.69, high: r = 0.70-0.89 and very high: r = 0.90-1.00.

To study the relation with neglect, first, all clinical and baseline characteristics from patients with visuo-spatial neglect were compared to patients without visuo-spatial neglect by using Wilcoxon rank sum test and Chi square tests. Second, the prevalence of somatosensory deficits in patients with visuo-spatial neglect was compared to the prevalence in patients without visuo-spatial neglect by using Chi Square tests. Severity of different somatosensory impairments was compared between patients with and without visuo-spatial neglect, using the Wilcoxon rank sum test. Finally, using the Fisher r-to-z transformation, it was tested whether the correlation coefficients for the association between somatosensory and motor impairments found in the patients with and without neglect were significantly different. P-values were considered statistically significant at the 0.05 level. All statistical analyses were performed using SPSS, version 22.

Results

One hundred twenty-two patients (n=122) were assessed from 12 days until six months post stroke (median 82 days, IQR 57-133). Table 1 shows the patient characteristics, presented for the total group, for the patients with visuo-spatial neglect (n=27, 22%) and without visuo-spatial neglect (n=95, 78%). For the total group, median age at stroke onset was 67 years (IQR 59-76) and 63% of the patients were males. The majority of patients suffered from ischemic stroke (88.5%). A total of 48 patients (39%) showed right-sided hemiparesis, 73 patients (60%) left-sided, and one patient had symptoms at both sides of the body.

Table 1. Patient Characteristics

	All patients (n=122)	Patients with neglect (n=27)	Patients without neglect (n=95)	p
Age stroke onset: median (IQR)	67 (58.8 -76.1)	68 (60.2-77.7)	66.7 (58.7-75.7)	0.646*
Gender, n (%)				0.376+
Male	77 (63.1)	19 (70.4)	58 (61.1)	
Female	45 (36.9)	8 (26.6)	37 (38.9)	
Days after stroke, median (IQR)	82 (57-132.8)	94 (64-169)	79 (56-123)	0.209*
Inpatient rehabilitation, n (%)	102 (83.6)	24 (88.9)	78 (82.1)	0.401+
Lateralisation, n (%)				0.033+
Right hemiparesis	48 (39.4)	5 (18.5)	43 (45.3)	
Left hemiparesis	73 (59.8)	22 (81.5)	51 (53.6)	
Both	1 (1.8)	0 (0)	1 (1.1)	
Type of stroke, n (%)				0.946+
Ischemia	108 (88.5)	24 (88.9)	84 (88.4)	
Haemorrhage	14 (11.5)	3 (11.1)	11 (11.57)	
Hand dominance, n (%)				0.251+
left	8 (6.6)	0 (0)	8 (8.4)	
right	113 (92.6)	27 (100)	86 (90.5)	
both	1 (0.8)	0 (0)	1 (1.1)	
CIRS: median (IQR)	6 (4-8)	7 (4-9)	6 (4-8)	0.244*
SCT: median (IQR)	27 (22.1)	29 (18-33)	52 (50-54)	< 0.001*
FMA-UE: median (IQR)	38 (7-59)	8 (5-58)	43 (10-60)	0.011*
MI: median (IQR)	67.5 (18-8.3)	23 (0-83)	76 (37-84)	0.016*
ARAT: median (IQR)	24.5 (3-54.3)	3 (0-43)	32 (3-56)	0.004*
Ad-AHA Stroke: median (IQR)	50.9 (14-79.8)	11 (0-77.8)	63.9 (17.9-88.4)	0.004*

IQR: Interquartile range, CIRS: Cumulative illness rating scale, SCT: Star cancellation test, FMA-UE: Fugl-Meyer motor assessment upper extremity, MI: Motricity index, ARAT: Action research arm test, Ad-AHA Stroke: adult-Assisting hand assessment stoke * Wilcoxon rank sum test, + Chi square test

Total group

Prevalence and distribution of somatosensory deficits

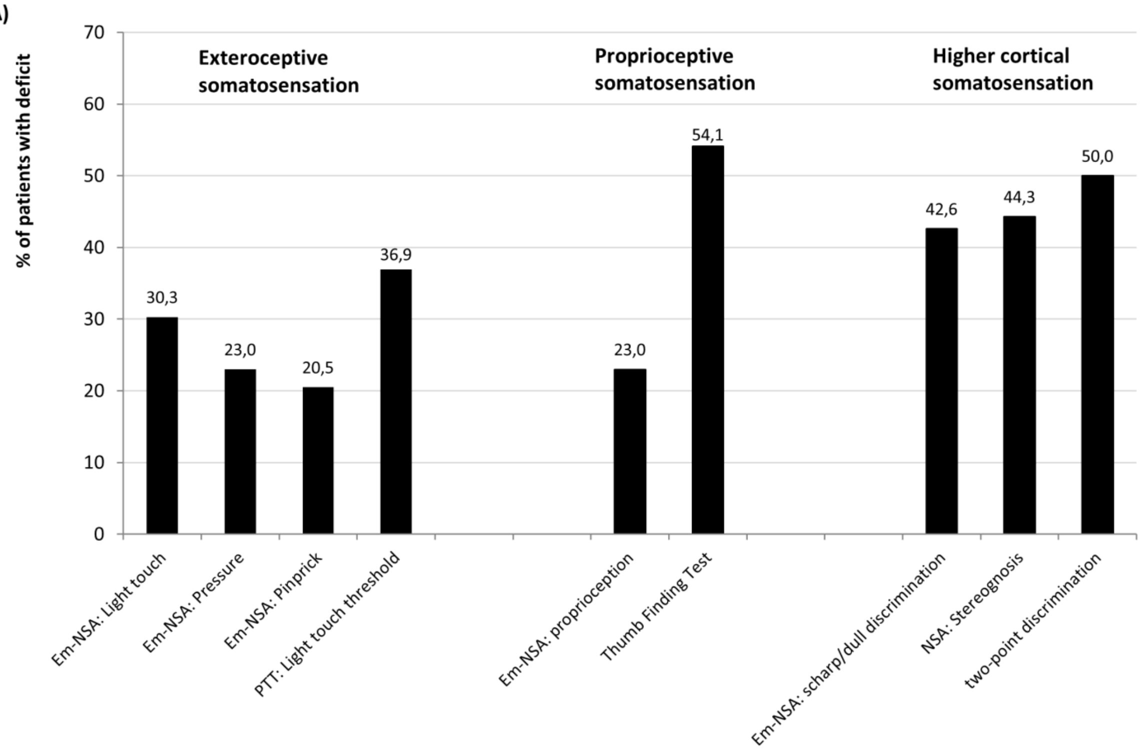
In the total group, exteroceptive impairments (light touch, pressure, pinprick, light touch threshold) were present in 21-37% of the patients, with the perceptual threshold of touch (PTT) revealing the highest frequency (37%) of exteroceptive dysfunction. Proprioceptive impairment (position sense, movement sense) was diagnosed in 23% of the patients when using the Em-NSA, whereas 54% of the patients showed proprioceptive impairment using the thumb finding test. Finally, deficits in higher cortical somatosensation (sharp-dull discrimination, stereognosis, two-point discrimination) were present in 43-50% of the patients (Figure 1, panel A). Panel B shows the distribution of somatosensory impairments according to the presence of unique (pure) exteroceptive, unique proprioceptive or unique higher cortical somatosensory impairments or a mixture of these deficits. This shows that only 16% of the patients presented without somatosensory impairment, and that approximately 50% of the patients experienced a mixture of somatosensory impairments. Therefore, only a minority of patients had unique exteroceptive (14%), unique proprioceptive (9%) and unique higher cortical somatosensory (13%) impairments.

Sensorimotor associations

Table 2 shows results of the correlation analysis between somatosensory and unimanual (FMA-UE, MI, ARAT) and bimanual (Ad-AHA Stroke) motor assessment for the total group. Overall, low correlations (r=.22-r=.44) were found between somatosensory and motor deficits, except for the perceptual threshold of touch (PTT) and stereognosis which showed moderate correlations with motor function (r=.51-r=.61). For each of the somatosensory variables, comparable results were found for the association with unimanual and bimanual motor function.

Figure 1. **A) Prevalence of exteroceptive, proprioceptive and higher cortical somatosensory deficits in the upper limb after stroke in all patients; B) distribution of somatosensory deficits: unique (pure) and mixed somatosensory impairments in all patients**

A)



B)

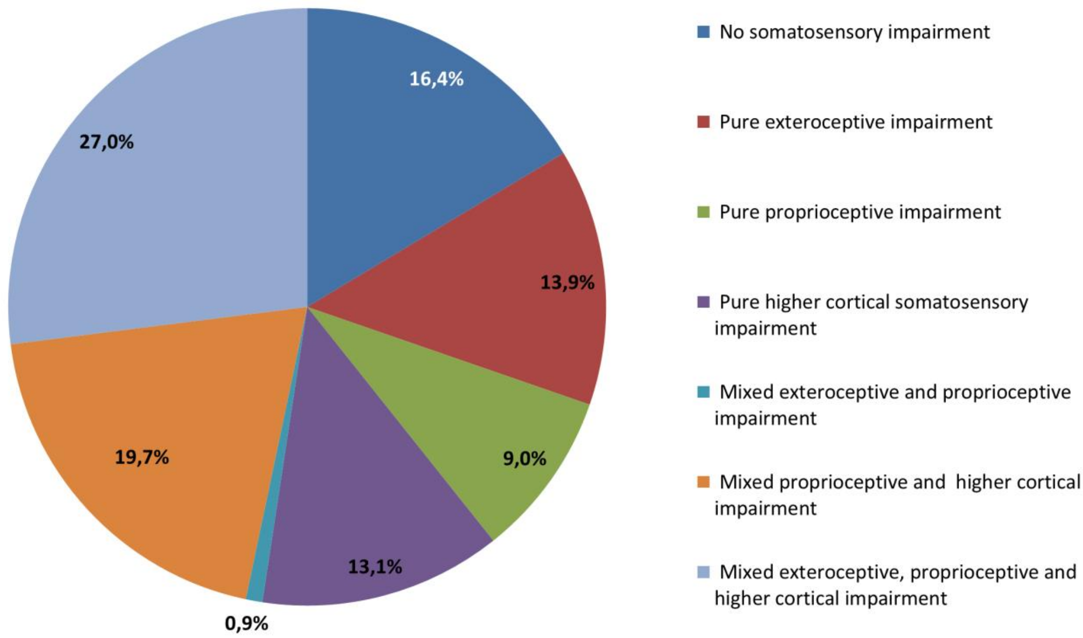


Table 2. Spearman rho correlation coefficients for association between somatosensory and motor impairments in all patients (n=122)

	FMA-UE	MI	ARAT	Ad-AHA Stroke
Exteroceptive somatosensation				
Em-NSA - Light touch	.309*	.318*	.386*	.372*
Em-NSA - Pressure	.329*	.337*	.382*	.371*
Em-NSA - Pinprick	.337*	.348*	.377*	.367*
PTT - Light touch	-.580**	-.564**	-.611**	-.608**
Proprioceptive somatosensation				
Em-NSA - Movement sense	.412*	.394*	.444*	.422*
TFT - Position sense	-.369*	-.354*	-.365*	-.389*
Higher cortical somatosensation				
Em-NSA - Sharp/dull discrimination	.223	.220	.312*	.282*
NSA - stereognosis	.514**	.535**	.599**	.530**
Two-point discrimination	-.316*	-.316*	-.403*	-.360*

Spearman rho correlation coefficients: Strength of the relation was indicated according to Munro[49]: very low: no indication, low: *, moderate: **, high: ***
FMA-UE: Fugl-Meyer motor assessment upper extremity, MI: Motricity index, ARAT: Action research arm test, Ad-AHA Stroke: adult-Assisting hand assessment stoke, Em-NSA: Erasmus MC modification of the (revised) Nottingham sensory assessment, PTT: Perceptual threshold of touch, TFT: Thumb finding test, NSA: Nottingham sensory assessment

Between-group differences in patients with and without visuo-spatial neglect

Prevalence and distribution of somatosensory deficits

Twenty-seven patients had visuo-spatial neglect, with a median score on the SCT of 29 (IQR 18-33). Twenty patients had visuo-spatial neglect in the left hemispace, four in the right hemispace and three had non-lateralised visuo-spatial neglect. As seen in table 1, patients with visuo-spatial neglect had significantly more often right hemisphere lesions and significantly more severe unimanual (FMA-UE, MI, ARAT) and bimanual (Ad-AHA Stroke) motor scores compared to patients without neglect. Figure 2 shows the prevalence (panel A) and distribution (panel B) of somatosensory impairments for patients with and without visuo-spatial neglect. Patients with neglect have significantly ($p<0.05$) more often somatosensory impairments (prevalence 41% to 78%) compared to patients without neglect (prevalence 15% to 47%) (Figure 2, panel A). The distribution analysis presented in panel B showed that in the neglect group, 7.4% had no somatosensory impairment, which is considerably less compared to the no-neglect group (18.9%). Furthermore, 74.1% of the patients with visuo-spatial neglect presented with mixed exteroceptive, proprioceptive or higher cortical somatosensory impairments, whereas only 40% presented with mixed impairments in the no-neglect group.

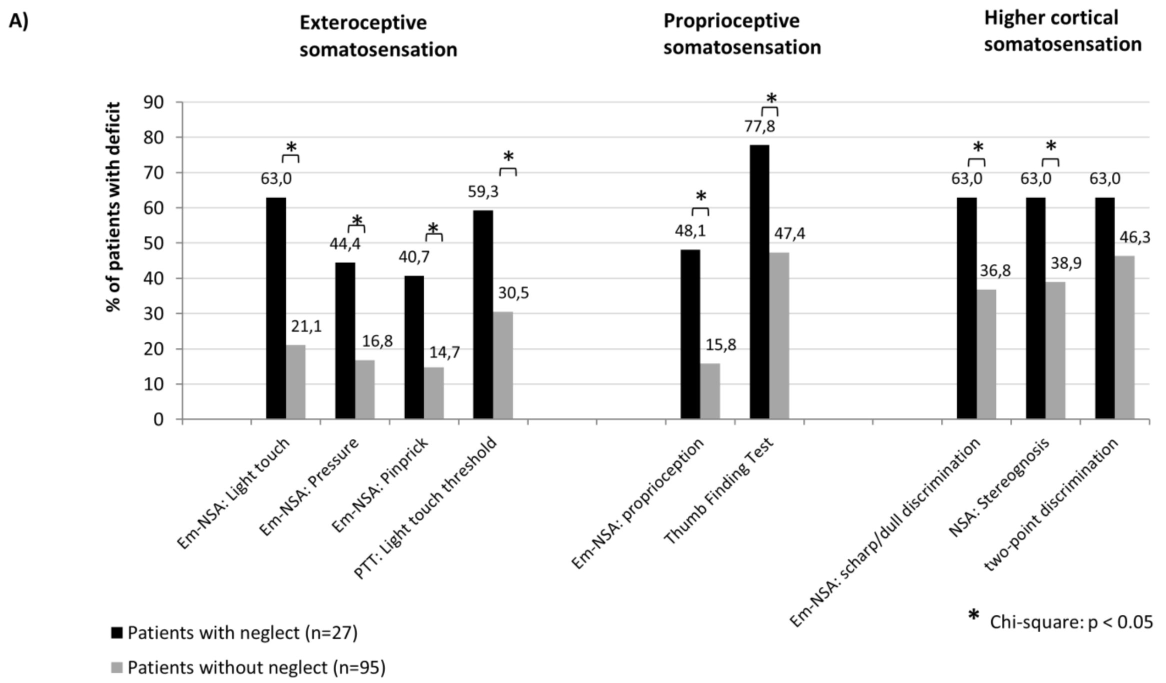
Severity of somatosensory impairments

Significant between-group differences in severity of the different somatosensory impairments are shown in Table 3. Exteroceptive (light touch, pressure, pinprick, light touch threshold), proprioceptive (position sense, movement sense) and higher cortical somatosensory (sharp-dull discrimination, stereognosis, two-point discrimination) functions were significantly ($p<0.05$) more severely affected in patients with visuo-spatial neglect.

Sensorimotor associations

The correlation analysis between somatosensory and uni- and bimanual assessment in patients with and without visuo-spatial neglect revealed overall stronger correlations in the neglect group (r=.44-r=.78) compared to the no-neglect group (r=.08-r=.59) (Table 4), with statistically significant between-group differences for the correlation of all motor scores (except for the ARAT), with stereognosis and pressure. On the other hand, the correlation between the perceptual threshold of touch (PTT) and all four motor outcomes, was comparable for patients with neglect (r=.46-r=.55) and without neglect (r=.55-r=.59). Furthermore, the association between somatosensory deficits and unimanual outcome (ARAT, FM-UE, MI) was comparable to the association with bimanual outcome (Ad-AHA Stroke). Finally, the highest values in correlation coefficients were found for the association between stereognosis and motor function in patients with neglect (r=.72-r=.78) as well as without neglect (r=.40-r=.51).

Figure 2. **A) Prevalence of exteroceptive, proprioceptive and higher cortical somatosensory deficits in the upper limb after stroke in patients with and without visuo-spatial neglect; B) distribution of somatosensory deficits: unique (pure) or mixed somatosensory impairments in patients with and without visuo-spatial neglect**



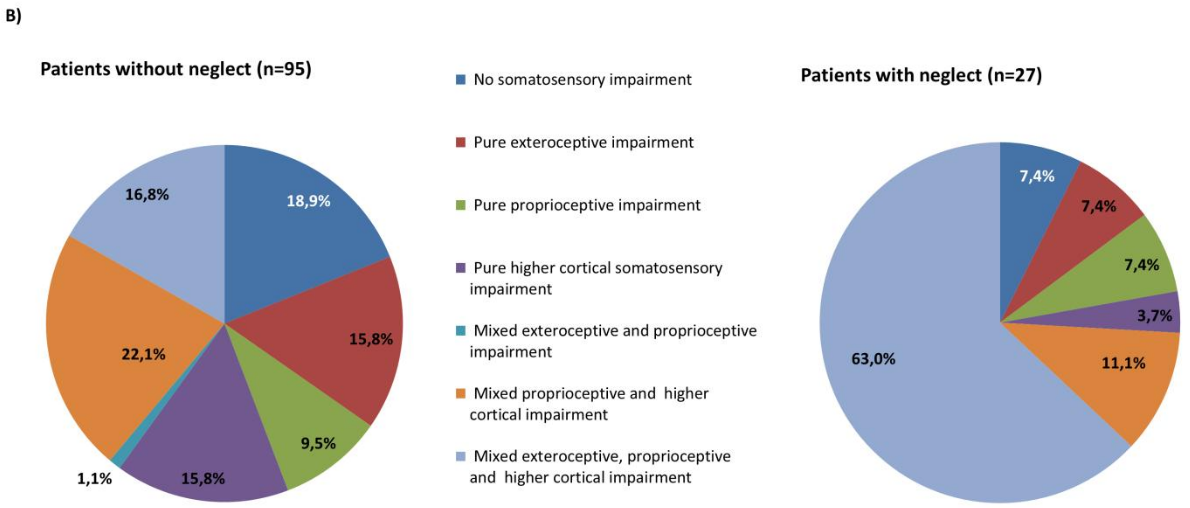


Table 3. **Differences in severity of somatosensory impairments in patients with and without visuo-spatial neglect**

	Patients with neglect (n=27) median (IQR)	**Patients without neglect (n=95)** median (IQR)	**P**
Exteroceptive somatosensation			
Em-NSA - Light touch	6 (0-8)	8 (7-8)	.000
Em-NSA - Pressure	8 (0-8)	8 (8-8)	.001
Em-NSA - Pinprick	8 (1-8)	8 (8-8)	.002
PTT – Light touch	7 (5-11)	4 (3.5-5.8)	.001
Proprioceptive somatosensation			
Em-NSA - Movement sense	7 (2-8)	8 (7-8)	.000
TFT - Position sense	1 (1-2)	0 (0-1)	.002
Higher cortical somatosensation			
Em-NSA - Sharp/dull discrimination	5 (0-8)	8 (5-8)	.002
NSA - stereognosis	1 (0-19.3)	19 (9.5-21)	.001
Two-point discrimination	16 (5-16)	5 (4-16)	.038

Em-NSA: Erasmus MC modification of the (revised) Nottingham sensory assessment, PTT: Perceptual threshold of touch, TFT: Thumb finding test, NSA: Nottingham sensory assessment, IQR: Interquartile range

Table 4. Spearman rho correlation coefficients for association between somatosensory and motor impairments in patients with and without visuo-spatial neglect

	FMA-UE			MI			ARAT			Ad-AHA Stroke		
	Neglect	No neglect	Fisher r-to-z p-value	Neglect	No neglect	Fisher r-to-z p-value	Neglect	No neglect	Fisher r-to-z p-value	Neglect	No neglect	Fisher r-to-z p-value
Exteroceptive somatosensation												
Em-NSA - Light touch	.517**	.203	0.110	.546**	.222	0.091	.511**	.307*	0.280	.556**	.257*	0.112
Em-NSA - Pressure	.574**	.137	0.024	.588**	.132	0.018	.572**	.214	0.059	.609**	.183	0.023
Em-NSA - Pinprick	.511**	.169	0.085	.565**	.164	0.039	.514**	.236	0.153	.598**	.201	0.034
PTT - Light touch	-.522**	-.546**	0.881	-.549**	-.546**	0.984	-.458*	-.593**	0.412	-.547**	-.550**	0.984
Proprioceptive somatosensation												
Em-NSA - Movement sense	.553**	.340*	0.242	.609**	.310*	0.091	.488*	.387*	0.582	.528**	.343*	0.317
TFT - Position sense	-.492**	-.261*	0.238	-.581**	-.234	0.063	-.437*	-.266*	0.395	-.514**	-.297*	0.254
Higher cortical somatosensation												
Em-NSA - Sharp/dull discrimination	.482*	.082	0.054	.495*	.082	0.044	.491*	.196	0.139	.462*	.150	0.129
NSA - stereognosis	.758***	.400**	0.013	.778***	.423*	0.010	.724***	.512**	0.126	.693**	.418*	0.075
Two-point discrimination	-.474*	-.246	0.250	-.477*	-.258*	0.267	-.457*	-.363*	0.624	-.536**	-.281*	0.177

Spearman rho correlation coefficients: Strength of the relation was indicated according to Munro[49]: very low: no indication, low: *, moderate: **, high: ***
FMA-UE: Fugl-Meyer motor assessment upper extremity, MI: Motricity index, ARAT: Action research arm test, Ad-AHA Stroke: adult-Assisting hand assessment stoke, Em-NSA: Erasmus MC modification of the (revised) Nottingham sensory assessment, PTT: Perceptual threshold of touch, TFT: Thumb finding test, NSA: Nottingham sensory assessment

Discussion

Results of this study showed that deficits in upper limb somatosensation are common in patients in the sub-acute phase post stroke and that these deficits are associated with unimanual and bimanual motor performance. It was shown that patients with neglect have more combined and more severe exteroceptive, proprioceptive and higher cortical somatosensory deficits compared to patients without neglect. Furthermore, this study showed that in patients with neglect, consistently stronger associations exist between somatosensory impairments and unimanual and bimanual motor performance, compared to patients without neglect.

Results of the study regarding the prevalence of somatosensory deficits are in line with previous studies. Connell et al.[6] reported that 23-47% experienced exteroceptive impairments in the upper limb, 43-63% proprioceptive impairments, and stereognosis was affected in 31-89% of the patients on admission to the rehabilitation centre. Tyson et al.,[7] reported that from a group of patients two to four weeks post stroke, 55% had exteroceptive dysfunction, whereas only 22% had proprioceptive dysfunction in the upper limb. This result might be explained by the inclusion of solely patients with an anterior circulation stroke, resulting primarily in deficits in the lower limb. Furthermore, the proprioceptive integration areas, located in the posterior parietal lobe in the brain,[52] were probably not affected by lesions in the anterior circulation. Interestingly, our study showed a large difference in prevalence of proprioceptive deficits when using the thumb finding test (54%) compared to the proprioception subscale of the Em-NSA (23%). This latter result might be explained by the difference in assessment methods. During the thumb finding test (TFT), position sense of the whole upper limb is assessed which might be more difficult compared to selective assessment of movement sense in separate joints in the Em-NSA.

As expected from our recent systematic review[9], this study showed that different somatosensory deficits are associated with motor impairments in the upper limb, especially the perceptual threshold of touch (PTT) and stereognosis, which showed moderate correlations with motor function. For each of the somatosensory variables, comparable results were found for the association with unimanual and bimanual motor function.

As hypothesized, the study showed that patients with visuo-spatial neglect present with more mixed somatosensory impairments and significantly more severe somatosensory impairments, compared to the no-neglect group. This finding could be explained by the extent of the lesion, as larger lesions will affect motor, somatosensory and attention areas in the brain. Patients with neglect had indeed, besides worse somatosensory outcomes, consistently worse motor outcomes. This might provide indirect evidence of larger brain lesions in patients with visuo-spatial neglect. Brain regions important in somatosensory processing, are also in close proximity to brain regions responsible for neglect. In a study of Ptak et al.,[23] visuo-spatial neglect was associated with damage to the temporal-parietal junction, the middle frontal gyrus and the posterior intraparietal sulcus, whereas Yue et al.,[53] showed that lesions in the inferior frontal gyrus, pre- and postcentral gyrus, superior and middle temporal gyrus, the insula and surrounding white matter, were more frequent in patients with visuo-spatial neglect compared to patients without neglect. These regions are in close proximity to the brain areas responsible for the processing of different somatosensory inputs such as the primary and secondary somatosensory cortex, insula and posterior parietal cortex.[2]

We acknowledge that the presence of visuo-spatial neglect might interfere with the assessment of somatosensory functioning due to the attention deficit. Therefore, the fact that patients with neglect have more mixed and more severe somatosensory impairments might also be attributed to the attention deficit. However, neglect was assessed using the SCT, a test for visuo-spatial extra-personal neglect, which is distinct from personal neglect,[22,54-56] of which the latter plausibly more strongly interferes with somatosensory testing. Furthermore, our sample included patients with visuo-spatial neglect without any somatosensory deficit, which supports that somatosensory function in patients with visuo-spatial neglect can be tested. Future research could use an integrative approach, combining different measures of neglect to capture all different dimensions of personal and extra-personal neglect using different paper-and-pencil tests and an extensive behavioral assessment such as the Catherine Bergego scale to study neglect during activities of daily living.[55-57]

Interestingly, the study also showed that in patients with neglect, the association between somatosensory and uni- and bimanual motor outcome is moderate to strong, compared to only low to moderate in the no-neglect group with significant between group differences for stereognosis and pressure perception. These findings may be important when delineating rehabilitation strategies, as patients with neglect might benefit from other types of treatment. Somatosensory function showed to be equally associated with both unimanual and bimanual motor performance. Finally, stereognosis showed to have the strongest association with motor function. This last finding is in accordance with results of a study of Connell et al.,[6] in which upper limb performance was found to be a significant predictor of stereognosis impairment. This correlation is not surprising as the recognition of objects relies on manual exploration to derive meaningful knowledge about the characteristics of the object. Assistance to manipulate the objects in the hand is given by the assessor, however it remains unclear whether patients derive the necessary perceptions by this method. Future studies are needed to gain insights in the validity of the stereognosis assessment in patients with severe hand paresis.

The strength of the current study is that it included the use of a combination of reliable and valid assessment methods for different somatosensory modalities of exteroceptive, proprioceptive and higher cortical functioning in a large cohort of subacute stroke patients. Furthermore, besides the pure clinical assessment methods, an increased objective measure to assess the exteroceptive function was included, namely the perceptual threshold of touch (PTT).[32] PTT measures the threshold of light touch in a more sensitive way by using high-frequency TENS which activates cutaneous receptors of light touch and their accompanying large myelinated Aβ fibres.[32] The clinical score of light touch and the PTT scores were significantly correlated ($r=-.63$) but our results suggest that the PTT assessment was able to identify more light touch deficits. This might have contributed to the finding that correlations between PTT and motor performance was the same for patients with and without visuo-spatial neglect. This highlights the potential of PTT as a measure of exteroceptive function in patients post stroke, both for research purposes and the clinical setting.

Some limitations of the study need to be recognized. First, patients were assessed in different settings: 84% of our patients were assessed in seven different rehabilitation centers and 16% were assessed at home but were still enrolled in outpatient physical therapy. Recruitment of patients was not consecutively, but was conducted in the different rehabilitation centers, upon eligibility on predefined assessment days. A flowchart cannot be provided as there is no data available on patients who were ineligible for participation in the study. The specific content and frequency of the treatment was not documented and therefore we were not able to control for treatment provided. Secondly, detailed information on localization and extent of the lesion would have been useful in exploring the shared neuro-anatomy between brain areas responsible for the outcomes of the study. Third, measurement of visuo-spatial neglect with solely the star cancellation test (SCT) might be seen as limited in order to assess this complex phenomenon. Yet, the emphasis of this study was on the somatosensory and motor functioning, with visuo-spatial neglect as an influencing factor. Future research is necessary to replicate these findings with a more extended test battery for personal and extra-personal neglect using a combination of different paper-and-pencil tests as well as behavioural assessment such as the Catherine Bergego Scale to assess neglect in daily activities.[57] Furthermore, we were not able to control for hemianopia as a confounding factor during the assessment of neglect, which could have influenced the results of the star cancellation test, due to a possible interfering visual impairment. Finally, sub-acute patients were assessed between 12 days and six months after stroke, which covers a broad time window for inclusion of the patients. Of our sample of 122 patients, 57% was in the early sub-acute phase (up to three months post stroke) and 43% was in the late sub-acute phase (between three and six months post stroke). As these groups were not comparable based on the different demographic and clinical characteristics, between-group analyses were not indicated. Future studies should report on repeated assessments at fixed time points.

Conclusions

The novel findings from this large cross-sectional study are that somatosensory deficits are frequently seen in the sub-acute phase post stroke, and related to motor outcome. The presence of visuo-spatial neglect is associated with the presence and severity of somatosensory deficits. Secondly, in patients with neglect, somatosensory impairments have a stronger association with motor impairments, when compared to patients without neglect. Therefore, recommendation for practice includes the screening of visuo-spatial neglect from the early stage post stroke. This might imply that patients with neglect need different intervention strategies for sensorimotor rehabilitation. Furthermore, as this study showed that somatosensory deficits are common after stroke, we suggest the clinical use of reliable and valid measures of somatosensory deficits. Additionally, quantitative measures such as PTT can be helpful in clinical practice.

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CHAPTER 4

Sensorimotor impairments in the upper limb at one week and six months post stroke

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Abstract

Background and Purpose: Longitudinal information regarding the prevalence of upper limb somatosensory deficits and the association with motor impairment and activity limitations is scarce. Therefore, the aim of this prospective cohort study was to map the extent and distribution of somatosensory deficits, and to determine associations over time between somatosensory deficits and motor impairment and activity limitations.

Methods: We recruited 32 participants who were assessed four to seven days post stroke, and at six months. Somatosensory measurements included the Erasmus-modified Nottingham sensory assessment (Em-NSA); perceptual threshold of touch (PTT); thumb finding test (TFT); two-point discrimination, and stereognosis subscale of the NSA. Evaluation of motor impairment comprised the Fugl-Meyer assessment, motricity index and action research arm test. Additionally, at six months, activity limitation was determined using the adult-assisting hand assessment stroke, the ABILHAND, and hand-subscale of the stroke impact scale.

Results: Somatosensory impairments were common, with 41-63% experiencing a deficit in one of the modalities within the first week and 3-50% at six months. In the acute phase, there were only very low associations between somatosensory and motor impairments (r=0.03-0.20), whereas at six months, low to moderate associations (r=0.32-0.69) were found for PTT, TFT and stereognosis with motor impairment and activity limitations. Low associations (r=0.01-0.29) were found between somatosensory impairments in the acute phase and motor impairments and activity limitations at six months.

Discussion and Conclusions: This study showed that somatosensory impairments are common and suggests that the association with upper limb motor and functional performance increases with time after stroke.

Introduction

Stroke is a leading cause of long-term disability.[1] In particular, two out of three survivors experience upper limb sensorimotor impairments resulting in limitations in functional arm use during daily activities.[2-4] An intact sensorimotor network has shown to be a prerequisite for purposeful arm use.[5] Therefore, a well interacting somatosensory and motor system is needed to perform functional arm and hand activities.

Somatosensation is defined as sensation arising from the skin, muscles and joints and is divided clinically into primary and secondary somatosensation.[6,7] The primary somatosensation includes exteroception and proprioception. Exteroception refers to tactile sensation such as touch, pressure, pain and temperature which originate in peripheral receptors located in the skin. Proprioception arises from the deeper tissues of the body, predominantly from the muscles, ligaments, tendons and joints and refers to position or movement sense of a body part. The secondary somatosensation, also called cortical somatosensation, includes two-point discrimination, stereognosis, graphesthesia and tactile localization. Cortical somatosensation involves discrimination of sensory stimuli and requires the primary sensory areas of the cortex to perceive the stimulus and the sensory association areas in the parietal lobe to interpret the meaning of the stimulus.[6,7]

Somatosensory deficits in the upper limb are common post stroke.[8-16] Clinically, reported prevalence rates range from 23-55% for exteroceptive impairments,[8-14] from 19-64% for proprioceptive impairments,[8,10,12-15] and up to 89% for cortical somatosensory deficits.[10,14,16] Differences in study populations, time post stroke, somatosensory modality tested, and assessment method used contribute to the variability in results.[17] In more recent studies, robotic-based measurements are used to quantify proprioceptive acuity or texture discrimination sense after stroke.[18-20] Although they provide reliable quantitative results, they are less applicable in clinical practice. Up until now, studies investigating somatosensory deficits mostly assessed patients in the sub-acute to chronic phase post stroke. Only three studies[13,15,16] reported on the extent of somatosensory deficits assessed clinically within the first week post stroke. Studies combining different measures to map exteroceptive, proprioceptive and cortical somatosensory deficits in the acute phase post stroke are missing. Also longitudinal follow-up of deficits in somatosensory function is scarce. Connell et al.[10] investigated somatosensory recovery in 70 stroke survivors from admission to a rehabilitation unit up to six months post stroke. The somatosensory recovery showed a similar pattern to the widely acknowledged motor recovery, with most recovery in the first weeks after stroke, and the recovery slope reaching a plateau between three and six months.[21] However, their study started from a variable point on admission to the rehabilitation centre and did not relate the recovery of somatosensory function to the recovery of motor function.[10]

Loss of somatosensory functioning post stroke has been related to decreased ADL independence,[8] and impacts on performance and perceived well-being during daily activities.[9] Cross-sectional studies reported a significant association between somatosensory deficits and upper limb motor performance,[11,22] pinch grip deficits,[23] and impaired bimanual coordination.[24] To date, only one study[13] reported on the change over time in associations between somatosensory functions and fine hand use in the first week, and at three and 18 months post stroke. A significant moderate association between fine hand use and both light touch and proprioception was reported at all three measurement points. In a number of recent systematic reviews,[25,26] somatosensory loss has been suggested as independent predictor of upper limb recovery. Despite these results, the reviews highlight the need for high-quality cohort studies that combine reliable and valid somatosensory measures of different modalities to determine the relationship with motor and functional performance. These insights are crucial for guiding and delineating treatment interventions for upper limb sensorimotor deficits post stroke.

Therefore, the aims of this study were firstly to map the prevalence and distribution of upper limb exteroceptive, proprioceptive and cortical somatosensory impairments within the first week and at six months. Based on previous findings, we hypothesized that somatosensory impairments are common, both within the first week and at six months, with the highest prevalence for higher order somatosensory deficits. We further hypothesize that the prevalence of different deficits will decrease over time during the course of spontaneous neurological recovery. Secondly, we wanted to determine the association between somatosensory deficits and motor impairment within the first week, and between somatosensory deficits and motor impairment and activity limitations at six months. A final objective was to define the association between somatosensory impairments within the first week and motor impairments and activity limitations at six months. We hypothesized, based on findings of Welmer et al.,[13] that somatosensory impairments are significantly related to motor impairment and activity limitations, both within the first week as at six months.

Methods

Subjects and setting

Participants for this prospective cohort study were recruited consecutively from the acute stroke unit of two University Hospitals in Belgium: University Hospitals Leuven and UCL Saint-Luc Brussels. Adults who had an acute (<1 week) first-ever stroke (as defined by the World Health Organization[27]) and who experienced a motor and/or somatosensory impairment in the upper limb and who showed sufficient cooperation to perform the assessment, were included in the study. Individuals were excluded if they had a pre-stroke Barthel index[28] score of <95 out of 100; other neurological conditions with permanent damage; a subdural hematoma, tumor, encephalitis or trauma that led to similar symptoms as a stroke; or serious communication, cognitive or language deficits, which could hamper the assessment. Participants signed a written informed consent form prior to participation. Ethical approval was obtained from the Ethics Committee of the University Hospitals Leuven and Brussels. Initially, 40 participants were enrolled in the study. Eight participants dropped out (5 deceased, 2 were medically unstable and 1 refused to participate) before the six-month assessment. Characteristics of participants who dropped out were statistically not significantly different from participants who were assessed at six months, except for a significantly higher age in the drop-out group. Thus, 32 participants were assessed at both time points and were included in the analysis. Median age at stroke onset was 68 years and 53% were males. The majority (84%) suffered from ischemic stroke and 72% showed left-sided hemiparesis.

Measures

Participants were assessed within the first week (4-7 days post stroke), and at six months. One trained researcher performed all data collection. First, patient characteristics were collected, including age at stroke onset, gender, comorbidities (cumulative illness rating scale, CIRS[29]), hand dominance (writing), time post stroke, stroke severity (National Institute of Health Stroke Scale, NIHSS[30]), type of stroke (ischemic or haemorrhagic), stroke lesion location according to affected vascular territory (anterior cerebral artery, middle cerebral artery, posterior cerebral artery or basilar artery), side of impairment and the presence of visuo-spatial neglect (star cancellation test, SCT[31]). Assessment of somatosensory and motor impairment was performed within the first week and again at six months post stroke. Additionally, at six months post stroke upper limb activity limitation was assessed.

Somatosensory impairment

The Erasmus MC modification of the (revised) Nottingham sensory assessment (Em-NSA)[32] was used to assess light touch (cotton wool), pressure (index finger), pinprick (toothpick), proprioception (movement sense) and sharp-dull discrimination (toothpick/index finger) impairment at predefined points of contact in the affected upper limb. Scores for each modality range from 0 (loss of function) to 8 (intact function). A cut-off score of <7 indicates the presence of somatosensory impairment. The Em-NSA has good to excellent intra-rater and inter-rater reliability.[32]

Position sense was examined using the thumb finding test (TFT).[33] The scoring ranges from 0 (no difficulty) to 3 (severe difficulty). A cut-off score of >0 indicates the presence of impaired proprioception (position sense). Psychometric properties of the TFT are not reported in literature and therefore, we performed a separate reliability study (unpublished data). For that study, a total of 43 patients with stroke were assessed within the first six months post stroke and the assessment of the TFT was videotaped. To determine the intra-rater reliability, videos were scored two times, after a minimum of one month in between the scoring. The intra-rater reliability was almost perfect, with a weighted kappa (95% CI) of 0.95 (0.89 to 1.00) and percentage of agreement of 95%.

Stereognosis assessment was based on the original NSA,[34] in which participants were asked to identify 11 common objects by touch and manipulation in the affected hand. When needed, assistance to the manipulation of objects in the hand was given by the assessor. Total scores range from 0 to 22. A cut-off score of <19 indicates the presence of stereognosis impairment. The stereognosis section of the NSA shows a moderate to good test-retest reliability in people with stroke.[35]

The perceptual threshold of touch (PTT)[36] is the minimal detectable stimulus level of touch. Therefore, a transcutaneous electric nerve stimulation (TENS) was applied with a portable device: A CEFAR Primo Pro (Cefar Medical AB, Sweden). Round electrodes (diameter 3 cm) were applied to the index finger and bulb of the thumb of the affected upper limb. A high-frequency constant current of 40Hz with single square pulses of 80µs pulse duration was applied. The amplitude was gradually increased from 0mA with increments of 0.5mA, until a tingling sensation is being perceived at the index finger. Good psychometric properties are established for the PTT, including excellent inter-rater and test-retest reliability.[36] To evaluate the PTT impairment, individual scores were compared to age- and gender-matched cut-off norm-values. PTT values for healthy participants range from 2.50-7.25 mA, determined by age, gender and side of assessment.[37]

Two-point discrimination (2PD)[38] was assessed at the fingertip of the affected index finger. Distance between the points was gradually reduced from 15 mm until the participant incorrectly felt only one point. The last correct answer was recorded as the result. The 2PD threshold in healthy controls has a mean of 3.5 mm (±SD 1.7).[16] Participants with a two-point discrimination threshold higher than 5 mm were classified as having impaired 2PD. Good reliability has been found for the 2PD assessment.[38]

Overall, exteroceptive somatosensation comprised the measures of light touch, pressure and pinprick (of the Em-NSA) and the perceptual threshold of touch. Proprioceptive somatosensation was evaluated using the thumb finding test and the proprioception subscale of the Em-NSA. Finally, cortical somatosensation was assessed by sharp-dull discrimination, stereognosis and two-point discrimination.

Motor impairment

The Fugl-Meyer assessment upper extremity (FMA-UE)[39] measures overall motor impairment, with a total score between zero (loss of motor function) and 66 (intact motor function). A cut-off score of <60 indicates the presence of motor impairment. The FMA-UE is considered valid and reliable.[39] The arm section of the motricity index (MI)[40] is a reliable measure of muscle strength during pinch grip, flexion of the elbow and abduction of the shoulder. Total scores vary between 0 and 100, with higher scores corresponding to better muscle strength. A cut-off score of <90 indicates impaired arm muscle strength. The action research arm test (ARAT)[41] assesses motor performance in 4 different subscales: grasp, grip, pinch and gross movement. The maximum score is 57, reflecting good motor performance. A cut-off score of <50 indicates the presence of fine motor impairment. Reliability[42] and validity[43] are established.

Upper limb activity limitation

The adult assisting hand assessment stroke (Ad-AHA Stroke)[44] is a Rasch-based performance scale which measures how effectively the affected hand is spontaneously used during performance of a bimanual functional task. Nineteen test items, describing different object-related hand actions result in total scores varying between 1 (no bimanual ability) and 100 (high bimanual ability). . The ABILHAND questionnaire[45] is a Rasch-based inventory of 23 uni- and bimanual activities that the participant was asked to judge as: 0 (impossible), 1 (difficult), and 2 (easy), irrespective of the limb(s) actually used to do the activity. The raw scores were then converted to logit-scores. Reliability, validity and minimal clinical detectible change has been established.[46,47] Using the hand subscale of the Rasch-based stroke impact scale (SIS), version 3[48], the participant needed to indicate the difficulty of 5 manual activities using the most affected hand such as carrying heavy objects, picking up a dime or turning the doorknob. The total score ranges from 0 to 100, with higher scores indicating better perceived hand function.

Statistical analysis

Clinical and demographic characteristics of participants both within the first week and at six months post stroke were displayed as frequencies with percentage, mean with standard deviation (SD) and median with interquartile range (IQR), as appropriate. A paired-sample Wilcoxon signed rank test was performed to assess changes over time for each of the somatosensory and motor impairment measures. The prevalence of deficits in different somatosensory modalities and in motor performance was calculated both within the first week and at six months, using frequencies with percentages. A distribution analysis of somatosensory impairments both within the first week as well as at six months was performed according to the presence or absence of exteroceptive, propriocepive or cortical somatosensory problems. Therefore, eight somatosensory categories were made: (1) no somatosensory impairment, (2) exteroceptive impairment, (3) proprioceptive impairment, (4) cortical somatosensory impairment, (5) mixed exteroceptive and proprioceptive impairment, (6) mixed exteroceptive and cortical somatosensory impairment, (7) mixed proprioceptive and cortical somatosensory impairment, and (8) mixed exteroceptive, proprioceptive and cortical somatosensory impairment. The prevalence of each of these categories was plotted in pie charts. Spearman rank correlation coefficients were used to assess (1) the association between somatosensory impairments and motor impairment within the first week, and (2) the association between somatosensory impairments and motor impairment as well as upper limb activity limitations at six months and (3) the association between somatosensory impairments measured within the first week and motor impairment as well as upper limb activity limitations at six months. Strength of the relation was interpreted according to Munro's correlation descriptors:[49] very low: r = 0.01-0.24, low: r = 0.25-0.49, moderate: r = 0.50-0.69, high: r = 0.70-0.89 and very high: r = 0.90-1.00. P-values were considered statistically significant at the 0.05 level. All statistical analyses were performed using SPSS, version 22.

Results

Table 1 shows the participant characteristics. Stroke severity was mild to severe with a median score on the NIHSS of 8. Visuo-spatial neglect was present in five participants. Overall, participants had poor upper limb motor function within the first week, with a median score of 15.5 out of 66 on the FMA-UE, of 41 out of 100 on the MI and of 3 out of 57 on the ARAT. Motor function improved significantly ($p<0.001$) at six months post stroke with median scores of 57, 79.5 and 53 on the FMA-UE, MI and ARAT, respectively. A similar pattern is seen for the somatosensory function, with poor upper limb somatosensory function within the first week, and with significant improvement at six months post stroke on all somatosensory outcome measures.

Figure 1 shows the prevalence of somatosensory impairments at both time points. Within the first week, exteroceptive impairments were present in 41-50% of the participants, whereas at six months only 3 to 22% of the participants had exteroceptive deficits. At that moment, PTT revealed the highest frequency of exteroceptive dysfunction. Second, proprioceptive impairment was diagnosed in 44% of participants when using the Em-NSA within the first week, and 63% of participants showed proprioceptive impairment using the TFT at that moment. At six months post stroke, the prevalence dropped to 3% when using the Em-NSA, whereas still 50% of participants had a position sense deficit assessed by the TFT. Finally, deficits in cortical somatosensation were present in 50-63% of participants early post stroke and decreased to 22-28% at six months.

Table 1. Participant characteristics (n=32)

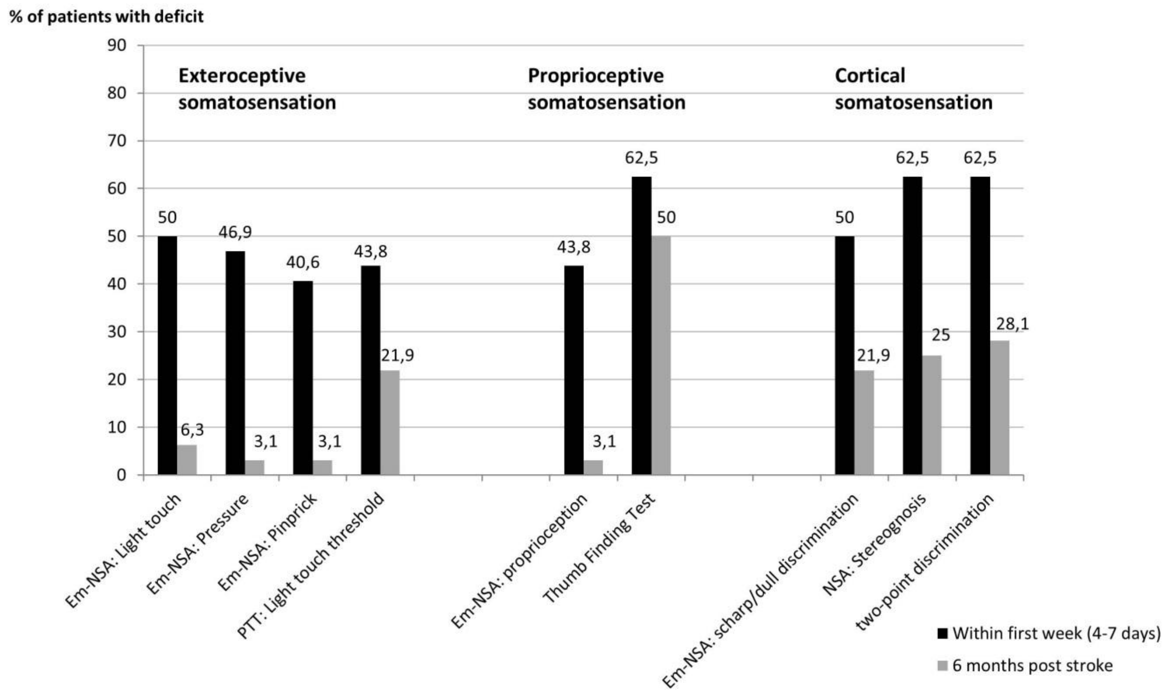
	Within 1 week	At 6 months	P*
Age stroke onset: median (Q_1-Q_3)	68.3 (61.3-80.1)		
Gender, n (%)			
Male	17 (53.1)		
Female	15 (46.9)		
Center, n (%)			
UZ Leuven	19 (59.4)		
UCL Brussels	13 (40.6)		
NIHSS: median (Q_1-Q_3)	8 (5-13)		
Lateralisation, n (%)			
Right hemiparesis	9 (28.1)		
Left hemiparesis	23 (71.9)		
Type of stroke, n (%)			
Ischemia	27 (84.4)		
Haemorrhage	5 (15.6)		
Vascular territory of stroke lesion, n (%)			
Anterior cerebral artery	1 (3)		
Middle cerebral artery	26 (81)		
Posterior cerebral artery	2 (6)		
basilar artery	3 (10)		
Hand dominance, n (%)			
left	2 (6.3)		
right	29 (90.6)		
both	1 (3.1)		
CIRS: median (Q_1-Q_3)	5.5 (4-8)		
Visuo-spatial neglect, n (%)	5 (16.1)		
Days after stroke, median (Q_1-Q_3)	6 (5-7)	183 (181-185)	
Exteroceptive somatosensation			
Em-NSA - Light touch: median (Q_1-Q_3)	6.5 (1.5-8)	8 (8-8)	<0.001
Em-NSA - Pressure: median (Q_1-Q_3)	8 (3-8)	8 (8-8)	0.001
Em-NSA - Pinprick: median (Q_1-Q_3)	8 (3-8)	8 (8-8)	0.001
PTT - Light touch: median (Q_1-Q_3)	5 (4-11)	3.5 (3-4.5)	<0.001
Proprioceptive somatosensation			
Em-NSA - Movement sense: median (Q_1-Q_3)	7.5 (4-8)	8 (8-8)	<0.001
TFT - Position sense median (Q_1-Q_3)	1 (0-2)	1 (0-1)	0.011
Cortical somatosensation			
Em-NSA - Sharp/dull discrimination: median (Q_1-Q_3)	6 (0-8)	8 (7-8)	<0.001
NSA - stereognosis: median (Q_1-Q_3)	6.5 (0-19.8)	21 (18.3-22)	<0.001
Two-point discrimination: median (Q_1-Q_3)	7 (4-16)	4.5 (3.3-6)	0.001

Table 1. *Continued*

	Within 1 week	At 6 months	P*
FMA-UE: median (Q_1-Q_3)	15.5 (2.3-54.8)	57 (10.3-63.8)	<0.001
MI: median (Q_1-Q_3)	40.5 (0-76)	79.5 (23.5-100)	<0.001
ARAT: median (Q_1-Q_3)	3 (0-31)	53 (3-57)	<0.001
ABILHAND logit score: median (Q_1-Q_3)		1.4 (-0.4-3.8)	
Ad-AHA Stroke: median (Q_1-Q_3)		75 (28-100)	
SIS hand function: median (Q_1-Q_3)		47.9 (16.7-95.8)	

* P value of Paired-Sample Wilcoxon Signed Rank Test, NIHSS: National institute of health stroke scale, CIRS: Cumulative illness rating scale, Em-NSA: Erasmus MC modification of the (revised) Nottingham sensory assessment, PTT: Perceptual threshold of touch, TFT: Thumb finding test, NSA: Nottingham sensory assessment, FMA-UE: Fugl-Meyer motor assessment upper extremity, MI: Motricity index, ARAT: Action research arm test, ABILHAND: ABILHAND questionnaire, Ad-AHA Stroke: Adult-assisting hand assessment stoke, SIS: Stroke impact scale

Figure 1. **Prevalence of somatosensory impairments in the upper limb within the first week and at six months post stroke**



The distribution of somatosensory impairments also changed over time (Figure 2). Within the first week, only 22% of participants had no somatosensory impairment, which increased slightly to 31% at six months (Figure 2, indicated in red). Furthermore, 66% of participants had mixed somatosensory impairments within the first week, whereas only 28% at six months (Figure 2, indicated in different types of green). At six months, more unique exteroceptive, proprioceptive or cortical impairments were present. At six months, there were less mixed forms of somatosensory impairments (Figure 2, indicated in different types of blue), especially proprioceptive impairments were present without other somatosensory impairments in 25% of the patients at six months compared to none of the patients within the first week.

Figure 2. **Distribution of somatosensory impairments in the upper limb within the first week and at six months post stroke**

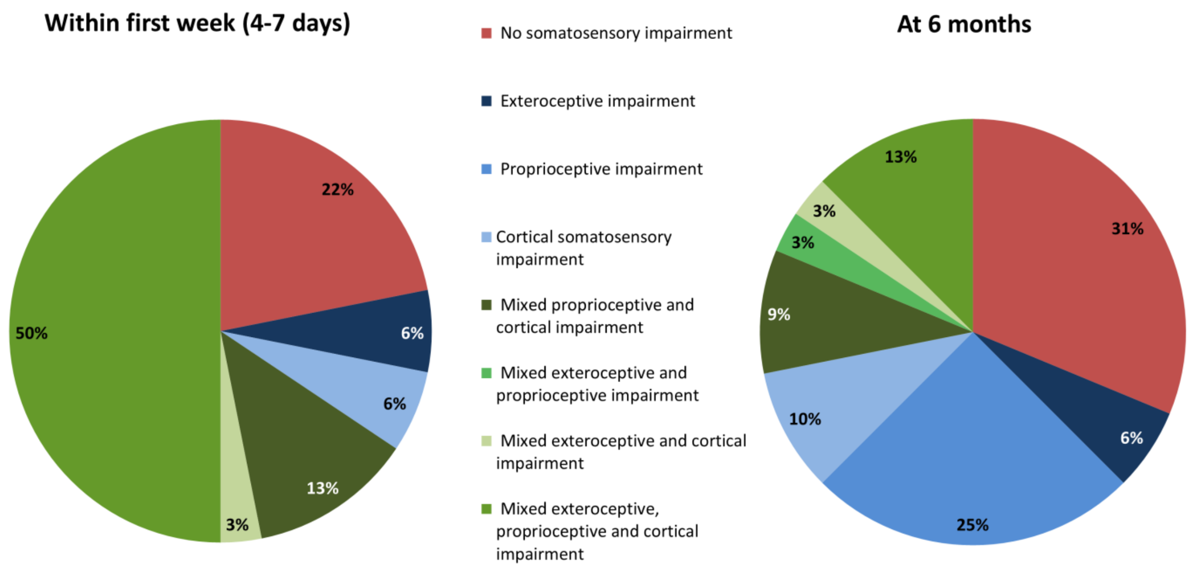


Figure 3 shows the prevalence of motor impairments at both time points. Within the first week, 30 patients (93.8%) have impaired motor function on all three motor outcome measures, whereas at six months post stroke, the prevalence of impairments drops to 43.8% on the ARAT, 53.1% on the FMA-UE and 62.5% has still motor impairments identified by the MI.

Figure 3. Prevalence of motor impairments in the upper limb within the first week and at six months post stroke

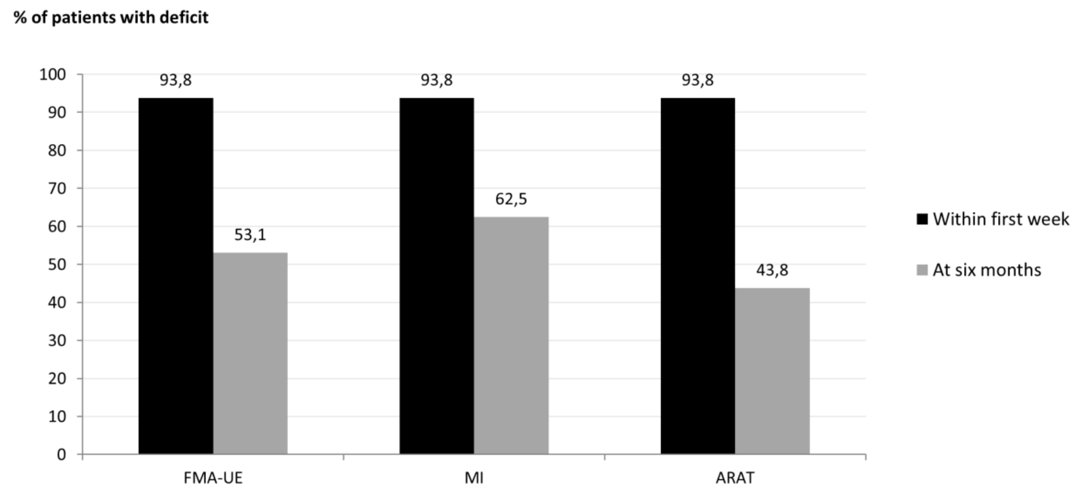


Table 2 shows the cross-sectional correlation analysis between somatosensory and motor impairment at both time points. Within the first week, only very low and non-significant associations (r=0.03 – 0.20) between somatosensory and motor impairment were found. At six months, low to moderate correlations were found for the association between motor impairments and different exteroceptive, proprioceptive and cortical somatosensory impairments. A worse performance on the somatosensory assessments was associated with worse performance on the motor assessments. For exteroceptive impairments, PTT showed moderate correlations with all motor impairment measures (r=-0.60 to -0.66) and proprioceptive impairments measured with both the TFT, as well as the movement sense scale of the Em-NSA showed low correlations (r=0.26 –0.39) with motor impairments. Finally, at the level of cortical somatosensory impairments, low to moderate correlations (r=0.37 – 0.56) were found for the link between motor function and stereognosis. A similar pattern was found for the association between somatosensory impairment and activity limitations at six months. Low to moderate correlations (r=0.32 – 0.69) were found for the association with PTT, TFT and stereognosis, again indicating that a worse performance on somatosensory assessments was associated with more limited upper limb activities.

Finally, the correlation analysis between somatosensory impairments measured within the first week and motor impairments and activity limitations at six months post stroke showed very low to low (r=0.01 – 0.29) associations.

Table 2. **Spearman rho correlation coefficients for cross-sectional associations between somatosensory and motor impairments within the first week and between somatosensory and motor impairments and activity limitations at six months post stroke**

	Within one week			At six months					
	Motor function			Motor function			Activity limitations		
	FMA-UE	MI	ARAT	FMA-UE	MI	ARAT	Ad-AHA Stroke	ABIL-HAND	SIS Hand Function
Exteroceptive somatosensation									
Em-NSA - Light touch	-0.05	-0.05	-0.06	0.02	0.05	0.20	0.23	0.20	0.18
Em-NSA - Pressure	-0.14	-0.16	-0.16	0.02	0.05	0.20	0.23	0.20	0.18
Em-NSA - Pinprick	-0.07	-0.10	-0.13	0.02	0.05	0.20	0.23	0.20	0.18
PTT - Light touch	-0.03	-0.04	-0.05	-0.64**	-0.60**	-0.66**	-0.67**	-0.67**	-0.69**
Proprioceptive somatosensation									
Em-NSA - Movement sense	-0.03	0.04	0.04	0.27*	0.27*	0.26*	0.31*	0.24	0.23
TFT - Position sense	-0.08	-0.15	-0.04	-0.48*	-0.39*	-0.37*	-0.36*	-0.35*	-0.32*
Cortical somatosensation									
Em-NSA - Sharp/dull discrimination	-0.20	-0.18	-0.13	-0.02	-0.03	0.13	0.13	0.03	0.09
NSA - stereognosis	0.06	0.18	0.08	0.41*	0.37*	0.56**	0.47*	0.46*	0.45*
Two-point discrimination	0.14	0.10	0.12	-0.07	-0.03	-0.19	-0.13	-0.19	-0.27*

Strength of the relation was indicated according to Munro[49]: very low: no indication, low: *, moderate: **
FMA-UE: Fugl-Meyer motor assessment upper extremity, MI: Motricity Index, ARAT: Action Research Arm Test, Ad-AHA Stroke: adult-Assisting Hand Assessment Stoke, ABILHAND: ABILHAND questionnaire, SIS: Stroke Impact scale, Em-NSA: Erasmus MC modification of the (revised) Nottingham sensory assessment, PTT: Perceptual threshold of touch, TFT: thumb finding test, NSA: Nottingham sensory assessment

Discussion

This study showed that somatosensory impairments are common in the acute phase post stroke, with prevalence rates of 41-63% for the different outcome measures of exteroceptive, proprioceptive and cortical somatosensory impairments. At six months post stroke, the prevalence of the different deficits decreases substantially. Overall, the distribution analysis showed that 78% of the patients experiences one or more somatosensory impairment within the first week, with mostly mixed exteroceptive, proprioceptive and cortical somatosensory deficits. Although many of the patients recover from different somatosensory impairments, still more than half of the patients have a remaining deficit at six months. Furthermore, we found that within the first week, there is a very low association between somatosensory and motor impairment. On the other hand, at six months low to moderate associations exist between different exteroceptive, proprioceptive and cortical somatosensory impairments and motor impairments and upper limb activity limitations. Finally, only very low associations were found for the association between somatosensory impairments within the first week and motor impairments and activity limitations at six months.

In the literature, information regarding the extent of somatosensory deficits in the upper limb in the acute phase is scant. Only three studies[13,15,16] reported on the prevalence of somatosensory deficits in the first week after stroke, but these did not assess several modalities, as our present study did. Light touch deficits were reported in 32%-50% of the patients,[13,15] proprioceptive deficits in 41%-50% of the patients,[13,15] and up to 85% had impaired somatosensory discrimination sense.[16] Comparable results were found in our sample, with 41-50% of the patients having exteroceptive dysfunction, 44-63% proprioceptive dysfunction and up to 63% experiencing a cortical somatosensory impairment within the first week.

Other studies reporting on the prevalence of somatosensory deficits assessed patients generally in the sub-acute and chronic phase post stroke, but again not combining the assessment of several modalities.[8-14] Regarding exteroceptive impairments in the chronic phase post stroke, two studies[9,11]identified light touch deficits in one out of three patients using the Semmes Weinstein monofilaments whereas, Welmer et al.,[13] reported that 19% of patients had a light touch deficit when assessed using a cotton wool. These results are again in line with our findings at six months. To the best of our knowledge, only one other study[50] reported on the prevalence of cortical somatosensory deficits in the chronic phase post stroke, confirming our result that still one out of four patients experience somatosensory discrimination problems at six months. Therefore, tackling these deficits might be of added value in upper limb stroke rehabilitation.

Two studies examined proprioceptive impairments in the chronic phase post stroke, with reported prevalence rates of 16-19%.[12,13] The proprioceptive assessment in our study showed impairment at six months in 3% when assessing movement sense with the Em-NSA, whereas a surprising 50% still had proprioceptive impairment when assessed with the thumb finding test. This latter result might be explained by the assessment method of the TFT. Position sense of the whole upper limb is assessed in the TFT, which might be more difficult compared to selective assessment of movement sense in separate joints in the Em-NSA. Another study of Hirayama et al.,[51] confirmed these results, as in their sample of 221 patients, 38% of the patients were identified with a proprioceptive deficit using the TFT, and only 13% when assessing movement sense in single joints. Goble et al.[52] further discussed several factors affecting proprioceptive acuity, which might also explain the difference in prevalence of proprioceptive deficits detected by both scales. During the TFT, the patient is asked to grasp his thumb with the contralateral hand, which might be compared to a contralateral position matching task (mirroring). Due to the involvement of both arms, it is difficult to ascertain whether the impairment arises from the hemiplegic arm, the non-hemiplegic arm, or both. Additionally, it was shown that contralateral matching requires interhemispheric communication through the transcallosal pathways of the corpus callosum.[52] This interhemispheric brain activation is less crucial during the execution of the Em-NSA measurement, as no contralateral arm movements are required. Additionally, normative values for the TFT of healthy elderly need to be determined, in order to assess the influence of age-related changes on the performance of this test.

Furthermore, our study adds to the current knowledge information from a cohort in which different somatosensory modalities, motor impairments and activity limitations were assessed within the first week and again at six months. The most striking result of this study is that somatosensory and motor impairments were not associated within the first week after stroke. This was in contrast to our hypothesis. Our hypothesis was driven by results of Welmer et al.,[13] reporting moderate correlations (r=0.56 – 0.59) between fine hand use, assessed with the nine hole peg test, and light touch and proprioception in the first week after stroke. These contradictory findings might first be explained by differences in study population. In the study of Welmer et al.,[13] 25 out of 66 patients (38%) showed severe motor impairment as indicated by the inability to pick up a peg. Furthermore, only one out of three patients showed to have impaired somatosensory function. This is different from our study sample, in which up to 60% of the patients showed no distal arm function on the ARAT scale, thus showing overall a more severely affected group of stroke survivors. Additionally, within the first week, 80% of our patients had a somatosensory deficit. As most of our patients had both very poor motor and somatosensory function in the acute phase, probably due to the cerebral shock phase, this might contribute to the very low association between somatosensory and motor function. Another possible explanation for the contradictory results is the difference in measurement of somatosensory impairments. In the study of Welmer et al.,[13] no standardized and reliable assessment method was used, and patients were only classified as having normal or impaired light touch and proprioceptive function. Furthermore, the authors computed Spearman rank correlations to assess the association between the continuous outcome on the nine-hole peg test and the dichotomized outcome for somatosensory functioning. However, this could be questioned, as the calculation of point-biserial correlation coefficients should be considered when addressing this relationship.[53]

At six months, we found low to moderate correlations for exteroceptive, proprioceptive and cortical somatosensory impairments with motor impairment and activity limitations. Overall, we found slightly stronger correlations compared to the literature. Up to now, studies concentrated mainly on outcomes at impairment level,[11,13,22,23] whereas our study adds to the body of knowledge information regarding the association between somatosensory impairments and activity limitations, using the ad-AHA stroke and perceived functional hand use post stroke, using the ABILHAND questionnaire and the hand subscale of the stroke impact scale. Finally, the correlation analysis between somatosensory impairments measured within the first week and motor impairments and activity limitations at six months post stroke showed only low associations. This is in contrast to a study by Au-Yeung et al.,[50] in which two-point discrimination ability at one week has shown to be predictive for achieving dexterity at three and six months post stroke, as defined by >35 points on the ARAT scale. This contrast might be explained by study population. In their study, only 32% of the subjects reached dexterity at six months, with a median score on the ARAT of 13.5 out of 57, whereas in our study, up to 63% of the patients reached dexterity, with a median score of 53 out of 57.

The high prevalence of different somatosensory impairments, both in the acute and chronic phase post stroke, and the important association at six months of several measures of exteroceptive, proprioceptive and cortical somatosensory impairments with both motor impairments and activity limitations in our study also points to the importance of measuring somatosensory deficits in the clinical setting with standardized, reliable and valid measures of somatosensory function, to accurately assess different somatosensory deficits. Knowledge of the extent and modality affected is the cornerstone for further developing realistic treatment goals and intervention strategies for the patient. The large change in modalities affected in the acute phase and at six months points to the necessity of future longitudinal studies with regular time points within the first six months to map the recovery of different somatosensory modalities over time. This would further increase our understanding of the evolution of somatosensory function in stroke patients underpinning sensory intervention strategies. Furthermore, sensorimotor treatment strategies should be developed and evaluated as the treatment of somatosensory deficits might also positively influence motor recovery.[17] A Cochrane review[54] on interventions for sensory impairment in the upper limb post stroke showed that multiple interventions for upper limb sensory impairment after stroke are described but up to now, there is insufficient evidence to support or refute their effectiveness in improving sensory or motor impairment or functional hand use. Based on our findings, we propose to use a set of three screening outcome measures, one for each of the following somatosensory categories, namely exteroceptive (PTT), proprioceptive (TFT) and cortical somatosensory functioning (stereognosis). The reason for the selection of these three outcome measures is two-fold. First, these outcome measures revealed the highest frequency of deficits, and therefore, these measurements could be more suitable in screening for small somatosensory deficits. However, important to notice is the fact that the TFT is only a coarse measure for somatosensory functioning (4-level ordinal scale),[33] and further research is warranted to examine the specificity of these outcome measures. Although a first attempt was made to establish intra-rater reliability of the TFT, the psychometric properties need to be further studied, including intra-rater, inter-rater and test-retest reliability, as well as different aspects of validity. Second, these outcome measures showed the strongest association with motor function and upper limb activity measures.

The novel aspect of this study relates to mapping the extent of different exteroceptive, proprioceptive and cortical somatosensory impairments in one cohort of patients, both within the first week, as well as at six months post stroke, using reliable and valid somatosensory clinical outcome measures. Furthermore, besides the pure clinical assessment methods, we used more objective measures to assess exteroceptive function, namely the perceptual threshold of touch (PTT), by using high-frequency TENS.[36] Finally, a full overview of the association between different somatosensory impairments and motor impairment as well as activity limitations is provided. Concentrating on the association between somatosensory function and these functional upper limb activity measures is new in this field of research. However, some limitations need to be considered when interpreting our results. First, patients were recruited in two different settings. We were not able to control for treatment provided. Furthermore, a flowchart of participant selection cannot be provided as there is no data available on patients who were ineligible for participation in the study. Secondly, this study had a restricted sample size, and therefore a multivariate prediction analysis was not conducted. It is therefore recommended to investigate the predictive value of different somatosensory deficits in the acute phase, besides other unmeasured factors such as mood, fatigue, motivation, leisure or employment status, on outcome at six months post stroke in a larger cohort study. Additionally, we were not able to investigate the influence of neglect on sensorimotor recovery, due to the small group of patients with neglect (n=5) in this study. Third, we included both patients with ischemic and hemorrhagic stroke. Nevertheless, only five patients had haemorrhagic stroke and exploratory statistical analysis performed only with data from patients with ischemic stroke, led to similar results (not presented in the results). Furthermore, patients presented with a large variety of stroke lesion locations, although, most in the middle cerebral artery territory. Future research is needed, including a larger number of patients with specific stroke topographic lesions, in order to further examine the influence of lesion location on different sensorimotor impairments.

Conclusions

Somatosensory impairments are common in acute patients post stroke, with mostly mixed exteroceptive, proprioceptive and cortical somatosensory deficits. Although many of the patients recover from different somatosensory impairments, still two out of three patients have remaining deficits at six months. In the acute phase, there is a very low association with motor impairment, whereas at six months, different somatosensory impairments are related to motor impairments and upper extremity activity limitations. Although no conclusions can be drawn on causality, our results suggest that the impact of somatosensory deficits on upper limb motor and functional performance increases with time after stroke. Therefore, recommendation for practice includes the assessment of somatosensory deficits with standardized, reliable and valid measures of somatosensory function, to accurately assess different somatosensory deficits as it will help guide and delineate realistic treatment goals and sensorimotor intervention strategies for the patient.

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CHAPTER 5

Voxel-based lesion-symptom mapping of acute stroke lesions underlying somatosensory deficits

Neuroimage: Clinical [under review]

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Abstract

The aim of this study was to investigate the relationship between stroke lesion location and the resulting somatosensory deficit. We studied exteroceptive and proprioceptive somatosensory symptoms and stroke lesions in 38 patients with first-ever acute stroke. The Erasmus modified Nottingham Sensory Assessment was used to clinically evaluate somatosensory functioning in the arm and hand within the first week after stroke onset. Additionally, more objective measures such as the perceptual threshold of touch and somatosensory evoked potentials were recorded. Non-parametric voxel-based lesion-symptom mapping was performed to investigate lesion contribution to different somatosensory deficits in the upper limb. Additionally, structural connectivity of brain areas that demonstrated the strongest association with somatosensory symptoms was determined, using probabilistic fiber tracking based on diffusion tensor imaging data from a healthy age-matched sample. Voxels with a significant association to somatosensory deficits were clustered in two core brain regions: the central parietal white matter, also referred to as the sensory component of the superior thalamic radiation, and the parietal operculum close to the insular cortex, representing the secondary somatosensory cortex. Our objective recordings confirmed findings from clinical assessments. Probabilistic tracking connected the first region to thalamus, internal capsule, brain stem, postcentral gyrus, cerebellum, and frontal pathways, while the second region demonstrated structural connections to thalamus, insular and primary somatosensory cortex. This study reveals that stroke lesions in the sensory fibers of the superior thalamocortical radiation and the parietal operculum are significantly associated with multiple exteroceptive and proprioceptive deficits in the arm and hand.

Introduction

Somatosensory deficits are common after stroke, with reported prevalence ranging from 11% to 85%.[1,2] While somatosensory symptoms after stroke may be discomforting and disabling by themselves, they further affect motor ability and overall rehabilitation after stroke. The somatosensory system plays a crucial role in motor performance by providing constant sensory feedback to be able to make adaptations in an on-going motor task.[3] As a consequence, somatosensory dysfunction represents an important factor for motor and functional outcome after stroke.[2,4]

Somatosensation comprehends all anatomical components of the central and peripheral nervous systems that receive and interpret sensory information from receptors in the joints, ligaments, muscles, and skin. The somatosensory system has two major primary functions: exteroceptive and proprioceptive sensation.[5] Exteroceptive sensation includes somatosensory modalities such as light touch, pressure, pinprick and pain[5], whereas proprioceptive sensation is the ability to recognize the location and movement of our limbs in space.[6] Although somatosensory symptoms are present in a large number of stroke patients, detailed reports on the affected components of somatosensation are rare.[1,2,7]

In contrast to the large amount of studies reporting on neural correlates of motor symptoms and recovery after stroke,[8,9] the relationship between lesion location and somatosensory deficits after stroke remains poorly understood. From primate studies, it is well known that the ventral posterior lateral nucleus of the thalamus is an important brain structure in somatosensory processing, as both the dorsal and the anterolateral ascending tracts terminate in this nucleus.[10] Most somatosensory information enters the cerebral cortex trough projections from the thalamus up to the primary somatosensory cortex (S1). Furthermore, small projections exist from the thalamus to the secondary somatosensory cortex (S2), the posterior parietal cortex and insular cortex.[11] In humans, lesion studies using structural brain imaging revealed contributions of thalamus, lenticulocapsular region, corona radiata, and the brain stem to the occurrence of a somatosensory deficit.[12,13] With respect to the secondary somatosensory cortex in the human parietal operculum, several distinct cortical subdivisions were distinguished for either basic sensorimotor processing or higher order somatosensory processing.[14,15]

To the best of our knowledge, only two recent studies investigated the voxel-wise association between lesion location and a somatosensory deficit in patients after stroke.[16,17] It was found that impaired light touch perception was associated with lesions in S2, the anterior and posterior insular cortex, the putamen, and white matter connections reaching ventrally towards prefrontal brain areas.[16,18] The other voxel-wise association study, including patients with insular strokes, demonstrated that lesions in the posterior insular cortex are associated exclusively to impaired temperature perception.[17] More detailed analysis of different somatosensory modalities has not been conducted as yet using modern voxel-based imaging methods. Thus, it remains unclear to what extent lesions in these brain areas affect other sensory modalities besides light touch and temperature perception. Therefore, the aim of the present study was to investigate, which brain regions are associated with the occurrence of different exteroceptive and proprioceptive somatosensory deficits in the acute phase after stroke, using voxel-based lesion-symptom mapping (VLSM).

Materials and Methods

Patients

Thirty-eight consecutive adult patients were recruited for this study at the acute stroke unit of two University Hospitals in Belgium from October 2012 until September 2014. The inclusion criteria were: (1) first-ever stroke (ischemic or hemorrhagic) as defined by the World Health Organization[19]; (2) assessment within the first week after stroke; (3) presence of motor and/or somatosensory deficit in the upper limb, using the Fugl-Meyer motor assessment upper extremity and somatosensory assessments as described below, and; (4) sufficient cooperation to perform the assessment. Patients were excluded if they: (1) had a pre-stroke Barthel Index < 95 out of 100; (2) had other serious neurological conditions with permanent damage; (3) had a subdural hematoma, tumor, encephalitis or trauma that led to similar symptoms as a stroke, and; (4) had serious communication, cognitive or language deficits, which could hamper the assessment. Patients signed a written informed consent form prior to participation. Ethical approval was obtained from the Ethics Committee of both University Hospitals in Leuven and Brussels.

Behavioral assessment

Testing procedure

Patients were assessed once within day 4 to day 7 after stroke onset using an MRI brain imaging protocol and clinical as well as more objective measures of somatosensory function. To ensure standardized data collection, the clinical testing was performed by only one trained physiotherapist (S.M.). Furthermore, patients' baseline characteristics were collected, and severity of stroke was assessed using the National Institutes of Health Stroke Scale (NIHSS). The presence of visuo-spatial neglect was assessed with the star cancellation test,[20] the most sensitive paper-and-pencil measure of visuo-spatial neglect. Different stimuli are presented on a piece of paper, including large stars, letters, short words and small stars. The test page is placed at the patient's midline. The task is to locate and cross out all small stars. A cut-off score of <44 (out of 54 stars) was used to determine the presence of visuo-spatial neglect.

Somatosensory assessment

Somatosensory deficits in the affected upper limb were assessed using the Erasmus MC modifications of the (revised) Nottingham sensory assessment, the perceptual threshold of touch (PTT), and somatosensory evoked potentials (SSEP).

The Erasmus MC modification of the (revised) Nottingham sensory assessment (Em-NSA) assesses light touch, pressure, pinprick and proprioception in the affected upper extremity and has good to excellent intra-rater and inter-rater reliability.[21] Light touch was applied with a cotton wool, pressure with the index finger and pinprick with a toothpick, all at predefined points of contact. Proprioception was assessed during passive movements of the different joints in the upper limb. Scores for each modality range on a continuous scale from 0 (complete loss of somatosensory function) to 8 (intact somatosensory function). A cut-off score of <7 indicates the presence of somatosensory deficit.

The perceptual threshold of touch (PTT)[22] is the minimal stimulus level of touch that is detectable. A transcutaneous electric nerve stimulation (TENS) was applied with a portable device, the CEFAR Primo Pro (Cefar Medical AB, Sweden). Round electrodes, with a diameter of 3 cm, were attached to the index finger and bulb of the thumb of the affected upper extremity. A high-frequency constant current of 40 Hz with single square pulses of 80 µs pulse duration was applied. The amplitude was gradually increased from 0 mA with increments of 0.5 mA, until a tingling sensation was perceived. To evaluate the PTT impairment, individual scores were compared to age- and gender-matched cut-off norm-values.[23] Impairment was defined as a threshold value above the predefined norm value and therefore PTT scores were classified into impaired or normal PTT. Good reliability has been established for this method in stroke patients.[22]

Somatosensory evoked potentials (SSEP) were measured following a standardized protocol.[24] A transcutaneous electrical stimulation (monophasic rectangular pulses) was delivered to the median nerve at the wrist with a pulse of 200 µsec and a stimulation rate of 5.1 Hz. Therefore, the cathode was placed between the tendons of the palmaris longus and flexor carpi radialis muscles, the anode was placed 2 to 3 centimeter distal to the cathode and the ground electrode was placed on the forearm. Sensory threshold was determined on the non-affected side and stimulation was performed at 3 times this sensory threshold for both the unaffected and the affected side. Stimulation was always above motor threshold and produced a clearly visible muscle twitch causing abduction of the thumb. Standard 10 mm cup electrodes, connected to a Medelec Synergy System, were placed at positions CP3 and CP4, according to the international 10-5 system.[25] The SSEP assessment was consecutively performed at the non-affected and the affected upper limb. The interside difference between interpeak cortical amplitude N20-P25 was calculated. To evaluate the SSEP impairment, these calculated scores were compared to norm-values of the interside difference of cortical amplitudes that were established in healthy persons with good reliability,[26] and were then classified into impaired or normal.

Imaging

Data acquisition

Magnetic resonance images of the brain were obtained with a Philips 3 T Achieve scanner. Either 3D or 2D fluid-attenuated inversion recovery imaging (FLAIR) data and diffusion-weighted images (DWI) were acquired at days 4 to 7 after stroke onset. Parameters settings for FLAIR sequences were: echo time = 350ms, repetition time = 4800ms, inversion time = 1650ms, field of view = 250×250mm², slice thickness = 1.12mm, and gap = 0.56mm. Parameter setting for DWI sequences were: echo time = 72ms, repetition time = 12s, b-value: 1300s/mm², slice thickness = 2.5mm, gap = 2.5mm.

Lesion segmentation

As established in previous stroke imaging studies, individual stroke lesions of the patients were segmented on FLAIR sequences.[27] Therefore, we used an in-house developed software tool for the analysis of stroke imaging series (Antonia, Analysis Tool for Neuro Imaging Data).[28] To this end, a rough region of interest (ROI) surrounding the hyperintense FLAIR lesion was drawn at each affected slice. In a subsequent step, a signal intensity threshold was manually applied to refine the final lesion segmentation. For hemorrhagic lesions, the perilesional edema was included into ROI, if restriction of diffusion was present. Accuracy of lesion delineation was inspected visually at each slice, and the corresponding diffusion-weighted images were consulted to confirm plausibility. All lesions were delineated by an experienced rater (S.S.K.). ROI from all slices were then concatenated to a volume of interest (VOI). FLAIR hyperintensities with no corresponding diffusion-restriction, representing leukoaraiosis or silent old stroke lesions (with no corresponding DWI lesion), were not included into the stroke lesion segmentation. Individual FLAIR datasets and lesion VOI were then registered to an in-house standard FLAIR brain template by linear transformation. This template has been previously created by normalization of FLAIR imaging data from 600 healthy volunteers in standard MNI (Montreal Neurological Institute) space (resolution of 2×2×2 mm³). The transformation parameters were then applied to the lesion VOI in order to ensure a standardized normalization for all individual stroke lesions.

Voxel-based lesion symptom mapping (VLSM)

Individual normalized FLAIR stroke lesions were entered into a voxel-based lesion-symptom mapping analysis using non-parametric mapping toolbox (NPM) from MRICron software package Version 6, 2013.[29] In our sample, the right hemisphere was affected in 28 patients, the left hemisphere in 10 patients. To increase statistical power of identifying a lesion pattern with a significant contribution to somatosensory deficits independent of the lesioned hemisphere, all lesion maps were flipped onto the right hemisphere, as reported before.[27] First, a lesion overlap was calculated to create a color-coded overlay map of injured voxels across all patients to provide an overview of all lesioned brain areas. Second, the statistical contribution of lesion location to somatosensory deficit was tested using voxel-based lesion symptom mapping. Therefore, in each voxel a group comparison between patients having a lesion in this voxel and patients having no lesion in this voxel was estimated as Brunner-Munzel rank order using the clinical somatosensory scores of the four Em-NSA subscales with the full score range (i.e. light touch, pressure, pinprick and proprioception) as dependent variables resulting in four different statistical maps.[29] For appropriate Brunner-Munzel statistics, only voxels affected in at least 10 patients were tested.[30] To correct for multiple comparisons, all result maps were corrected using a threshold of 1% false discovery rate (FDR). In order to visualize the spatial distribution of brain voxels contributing to disturbance of the different somatosensory modalities, the four statistical maps from the somatosensory tests (light touch, pressure, pinprick and proprioception) were binarised at the threshold of significance (1% FDR) and overlaid. To describe key anatomical regions involved in somatosensory deficit, the peak voxel clusters were then identified from global maxima of the overlay map. These peak voxels were used as starting points for probabilistic fiber tracking (see below). Only for the PTT and the SSEP, dichotomous scores were entered into another VLSM analysis and Liebermeister statistics were estimated. For the PTT, a correction for multiple comparison was applied at a level of 1% FDR. For exploratory reasons, a more lenient threshold of 5% FDR was applied for results of SSEP, due to the higher rate of missing values of the SSEP variables.

Probabilistic fiber tracking

In healthy volunteers, we investigated connection probability of brain regions showing significant associations with somatosensory deficits using the probabilistic diffusion models and tractography implemented in the FMRI Software Library (FSL) software package 5.1 (http://www.fmrib.ox.ac.uk/fsl).[31] To this end, we acquired diffusion weighted imaging data from 24 healthy, age-matched volunteers (mean age: 67 years, range: 32 to 78 years; unpaired t-test of age to current study sample of 38 patients: $p = 0.4$). A 3T Siemens Skyra MRI scanner (Siemens, Erlangen, Germany) and 32-channel head coil were used. 75 axial slices were obtained covering the whole brain with gradients (b=1500 mm²/s) applied along 64 non-collinear directions with the sequence parameters: Repetition time = 10000 ms, echo time = 82 ms, field of view = 256×204, slice thickness = 2 mm, in-plane resolution = 2×2 mm². All datasets were corrected for eddy currents and head motion. Peak clusters resulting from Brunner-Munzel tests (x/y/z = 29/-25/25 and 35/-15/16) were used to generate a cubic cluster of 5×5 voxels using toolboxes provided by FSL. From each voxel, 10000 samples were initiated through the probability fiber distribution of principle white matter fiber directions with a curvature threshold of 0.2. Resulting tract distributions were normalized in relation to the general connectivity profile in each individual volunteer. We applied a threshold of 100 samples (1% of 10000 samples) following recommendations from the online documentation of the FSL library. Resulting tracts from all 24 volunteers were then registered to MNI space using the linear and non-linear transformation tools implemented in FSL.[32] A common tract was created using voxels that were found in at least 50% (12 of 24) of the participants. For anatomical comparisons, individual pyramidal tracts were additionally created analogously using the precentral cortex as seeding mask and waypoints in the posterior internal capsule and cerebral peduncle.

Results

We recruited 38 patients from two acute stroke units with a median of 6 days post stroke (range 4-7) (Table 1). The median age at stroke onset was 75 years (IQR 63-81) and 53% of the patients were males. The majority of the patients suffered from ischemic stroke (87%), whereas five patients presented with primary intracranial hemorrhage. A total of 28 patients

(74%) had a lesion in the right hemisphere, and ten patients (26%) a lesion in the left hemisphere. Stroke severity was mild to severe with a score range on the NIHSS of 1 to 23, and a median score of 8.5 (IQR 6-13). Neglect was present in 8 patients (23%). A total of 20 patients (53%) had a light touch deficit, 19 (50%) had a pressure deficit, 17 (45%) had a deficit in pinprick sensation, and 19 (50%) had impaired proprioception. Finally, deficits in the perceptual threshold of touch were present in 65% of the patients, whereas 23% had impaired SSEP. Further detailed information on the patient characteristics is shown in Table 1.

Table 1. Patient Characteristics (n=38)

Age stroke onset, years: median (IQR)	74.7 (62.8 -80.6)
Gender, n (%)	
Male	20 (52.6)
Female	18 (47.4)
Days after stroke, median (IQR)	6 (5-7)
Affected hemisphere, n (%)	
Left	10 (26.3)
Right	28 (73.7)
Type of stroke, n (%)	
Ischemia	33 (86.8)
Hemorrhage	5 (13.2)
Hand dominance, n (%)	
Left	1 (2.6)
Right	37 (97.4)
Stroke severity (NIHSS): median (SD)	8.5 (6-13)
Visuo-spatial neglect (n=35), n (%)	8 (22.9)
Em-NSA- light touch (/8): median (IQR)	6 (0-8)
Em-NSA- pressure (/8): median (IQR)	7 (2-8)
Em-NSA- pinprick (/8): median (IQR)	8 (3-8)
Em-NSA- proprioception (/8): median (IQR)	6.5 (3.75-8)
Deficit in all 4 Em-NSA subscales	16 (42)
Deficit in 1, 2, or 3 Em-NSA subscales	6 (16)
No deficit in Em-NSA subscales	16 (42)
PTT deficit (n= 37): n (%)	24 (64.9)
SSEP deficit (n= 30): n (%)	7 (23.3)

IQR: interquartile range, NIHSS: National Institutes of Health Stroke Scale, Em-NSA: Erasmus MC modification of the (revised) Nottingham sensory assessment, PTT: perceptual threshold of touch, SSEP: somatosensory evoked potentials

The overlay of the stroke lesions of all patients showed a wide distribution across the entire hemisphere including all four brain lobes and the brain stem. In particular, areas of the middle cerebral artery territory were affected. Subcortical areas such as corona radiata, extreme, external, and internal capsule, claustrum, basal ganglia, thalamus, as well as insular and opercular cortex were most frequently involved (Fig. 1).

Figure 1 **Lesion overlay plot**

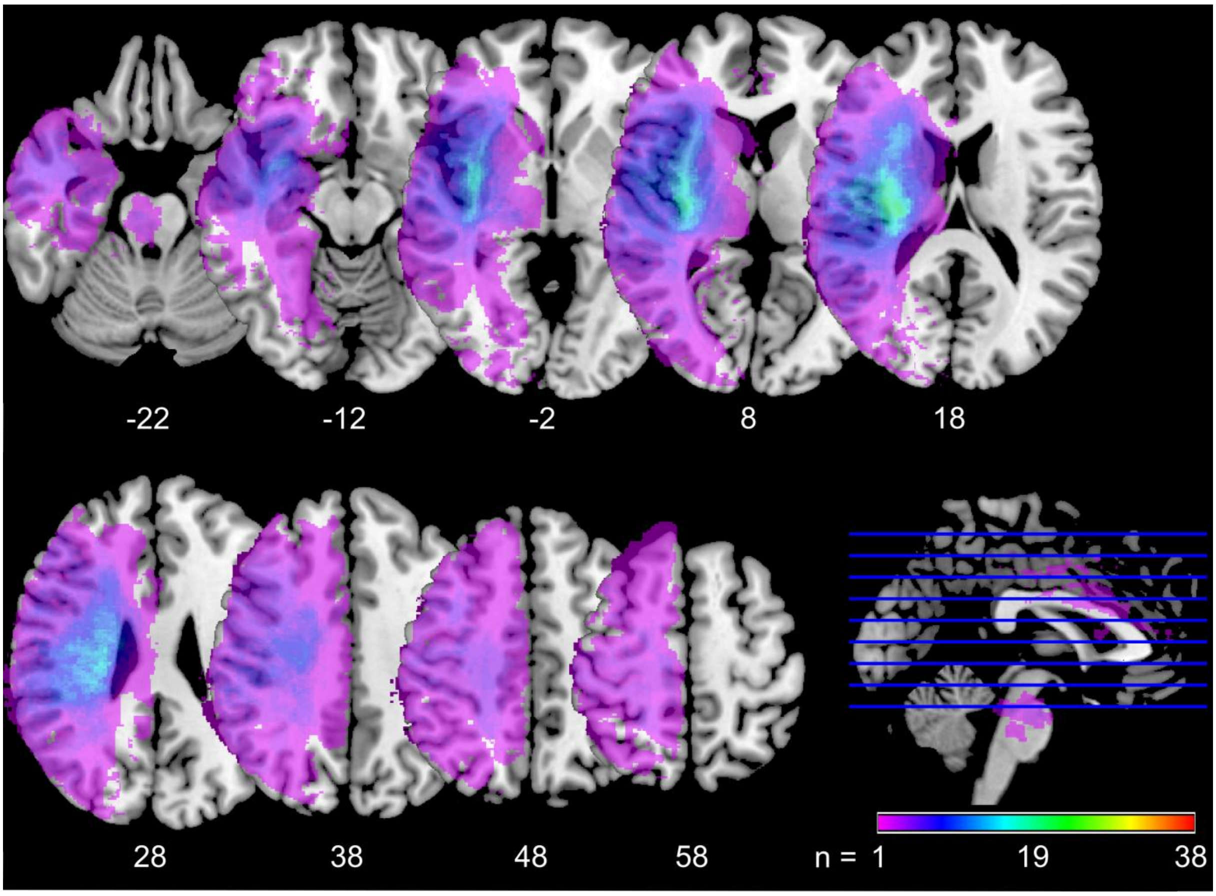

Figure 1 shows an overlay map of individual stroke lesions of all 38 patients. Maps are overlaid on a T1-template in MNI space 1 × 1 × 1 mm³. All lesions were flipped to the right hemisphere. MNI coordinates of each transverse section (z-axis) and a sagittal slice for visualization are given. Color scale indicates the number of patients having a lesion in this voxel. Stroke lesions are distributed across the entire hemisphere. Most frequently lesioned voxels are found in the insula, the corona radiata, and in the striatocapsular region.

Fig. 2 shows the statistical maps of the VLSM analysis of the four Em-NSA subscales. Lesions in the parietal subcortical white matter, the dorsal internal capsule, and in the insular and opercular cortex were associated with deficits in all four somatosensory modalities (Table 2). The extent and distribution of significant voxels, however, differed slightly between the four Em-NSA tests. The largest area of significant voxels covering 18.5 ml was found for light touch deficits including the parietal white matter parts of the corona radiata inferior to the post- and precentral gyri, the parietal operculum, the insular cortex, and the external, dorsal internal, and extreme capsule. Significant voxels associated to a pressure deficit comprised a volume of 9.7 ml including similar regions as for light touch, but with lesser involvement of the frontal parts of the external and extreme capsule and the insular cortex. Maximal association was found in the parietal operculum and the parietal white matter of the corona radiata, inferior to the post- and precentral gyrus. Voxels associated with pinprick deficits were found in the parietal operculum as well as in parts of the insular cortex and the white matter inferior to the post- and precentral gyri comprising a volume of 2.9 ml. Finally, the test for proprioception deficit identified the smallest number of voxels adding up to a volume of 1.4 ml, including the corona radiata inferior to the post- and precentral gyrus as well as small parts of the parietal opercular and the dorsal insular cortex (Table 2). Overlay maps of voxels contributing to symptoms in the four somatosensory modalities identified two brain regions showing significant associations in all four tests: the white matter in parietal lobe near the central region (maximum in the MNI-coordinate 29 / -25 / 25 mm) and the parietal operculum close to the insular cortex (maximum in the MNI-coordinate 35 / -15 / 16 mm) (see Fig. 2).

Fig. 2 Voxel-based statistical analysis of lesion impact on somatosensory deficit of light touch, pressure, pinprick, and proprioception

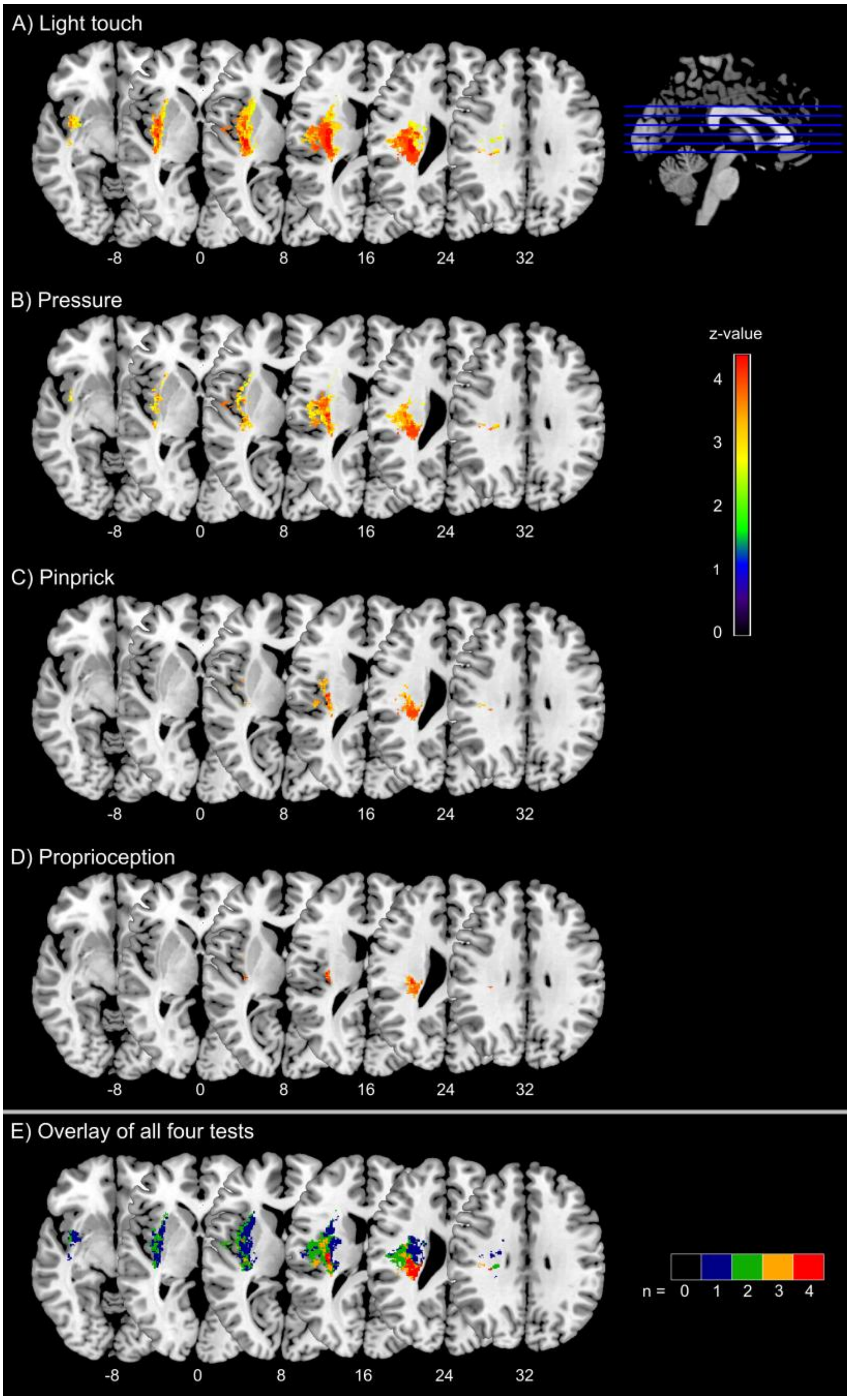

Figure 2 shows voxels with significant association in lesion-symptom mapping to four somatosensory tests: **2A) Light touch, 2B) Pressure, 2C) Pinprick, and 2D) Proprioception.** Color scale indicates Brunner-Munzel rank order z-statistics. **2E shows an overlay of all four tests.** Color scale indicates for each voxel the number of somatosensory tests for which a significant association was seen in case of a lesion in this voxel.

Table 2. Lesion locations associated to somatosensory deficit.

Tested Symptom	MNI coordinates (mm) X	Y	Z	Brain region	Z-score
Light Touch	29	-25	25	Superior thalamocortical radiation	7.2 **
	34	-7	18	S2 / Parietal operculum	7.1 **
	34	-14	16	Insulo-opercular cortex	6.8 **
	29	-23	25	STR	6.6 **
	33	-5	13	External capsule	6.2 **
	33	-19	21	S2 / Parietal operculum	5.1 **
	35	-15	16	S2 / Parietal operculum	3.9 **
	42	-35	27	Inferior parietal lobule	3.9 **
	28	-21	12	CST	3.5 **
	28	-5	10	Putamen	3.2 **
	27	-19	14	Posterior limb of internal capsule	3.1 **
Pressure	34	-14	16	Insulo-opercular cortex	4.9 **
	29	-25	25	STR	4.8 **
	32	-22	23	S2 / Parietal operculum	4.0 **
	35	2	2	External capsule	3.7 **
	29	-21	12	Posterior limb of internal capsule	3.4 **
	37	-12	12	Insular cortex	3.1 **
	46	-14	18	S2 / Parietal operculum	3.1 **
	28	-21	12	CST	3.1 **
	30	-6	12	Putamen	2.7 **
Pinprick	32	-22	23	S2 / Parietal operculum	4.3 **
	29	-25	25	STR	4.3 **
	34	-15	16	Insulo-opercular cortex	4.2 **
	29	-21	23	CST	3.7 **
	42	-35	27	Inferior parietal lobule	3.7 **
	29	-21	12	Posterior limb of internal capsule	3.1 **
	35	2	2	External capsule	2.6 **
Proprioception	32	-20	15	S2 / Parietal operculum	4.6 **
	29	-25	25	STR	4.6 **
	34	-14	16	Insulo-opercular cortex	4.4 **
	32	-21	17	S2 / Parietal operculum	3.9 **
	27	-21	24	CST	3.7 **
PTT	34	-14	15	Insulo-opercular cortex	-4.0 ++
	34	-6	15	S2 / Parietal operculum	-3.9 ++
	31	-22	18	S2 / Parietal operculum	-3.9 ++
	29	-24	25	STR	-3.5 ++
	36	-13	2	External capsule	-3.2 ++
	31	5	5	Putamen	-3.0 ++
SSEP	30	-12	14	S2 / Parietal operculum	-3.7 +
	29	-24	25	STR	-3.7 +
	34	-17	16	S2 / Parietal operculum	-3.4 +
	29	-16	12	Posterior limb of internal capsule	-3.2 +
	35	3	2	External capsule	-2.3 +

PTT: perceptual threshold of touch, SSEP: somatosensory evoked potentials, S2: secondary somatosensory cortex, STR: superior thalamocortical radiation, CST: corticospinal tract **: significant based on Brunner-Munzel Z-score after applying a FDR of 0.01. For dichotomous variables, Liebermeister Z-scores are indicated with a double cross (++) for FDR 0.01 or a single cross (+) for FDR 0.05.

Probabilistic fiber tracking demonstrated that the parietal subcortical white matter region shows strong connections to projection fibers from the dorsal brain stem through the dorsal internal capsule and thalamus up to the postcentral gyrus (Fig. 3, golden tract). This pathway matches the anatomical course of the ascending sensory tract. In addition, a frontal associative connection along the external capsule and a connection to the cerebellum could be identified (Fig. 3, golden tract). The structural connectivity of the second, opercular region revealed an association pathway from the thalamus to the parietal operculum and the insular cortex which corresponds to sensory fibers from thalamus to the secondary somatosensory cortex as well as connections to the primary somatosensory cortex (Fig. 3, green tract).

Fig. 3 Fibre tracking results starting from core brain regions in 24 age-matched healthy controls

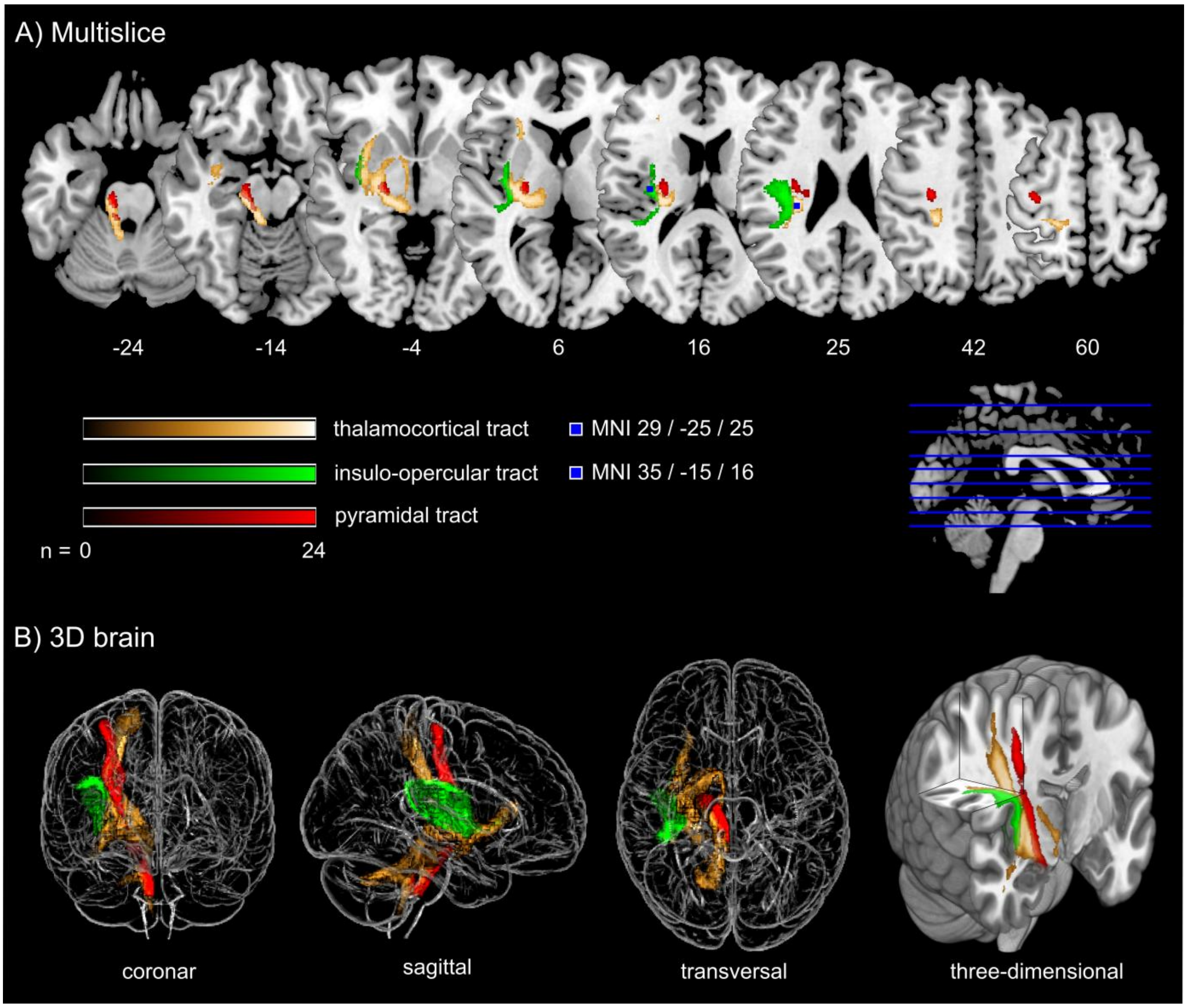

Figure 3 shows three different probabilistic fiber tracts, taken from 24 healthy age-matched volunteers demonstrating structural connectivity of the two core regions of somatosensory lesion-symptom mapping in relation to the pyramidal tract. The golden and the green pathway were tracked based on the VLSM results from the somatosensory tests (figure 2): the two peak coordinates from the two core regions showing an overlap in VLSM-analysis for all four somatosensory modalities were entered as seed coordinates for probabilistic fiber tracking (MNI coordinates 29/-25/25 and 35/-15/16). For anatomical comparison, the pyramidal tract is shown in red color. In A), maps are overlaid on a T1-template in MNI space 1 × 1 × 1 mm³. MNI coordinates of each transverse section (z-axis) and a sagittal slice for visualization are given. Color scales indicate the number of volunteers presenting the tract in this voxel. The two blue squares in transverse sections (z=16 and z=25) display the seed coordinates which were taken for the fiber tracking. In B), a 'glass brain' visualization and a half-split three-dimensional model of the three tracts is shown.

The VLSM analysis of the PTT and SSEP showed a similar pattern of lesion distribution with significant association to abnormalities in these tests (Fig. 4). Voxels from the parietal opercular cortex, the insular cortex, the internal and external capsule and the thalamocortical tract showed association to a deficit in PTT. Voxels in the thalamocortical tract showed an association to deficits in SSEP (Table 2).

Fig. 4 Voxel-based statistical analysis of lesion impact on perceptual threshold of touch and somatosensory evoked potentials

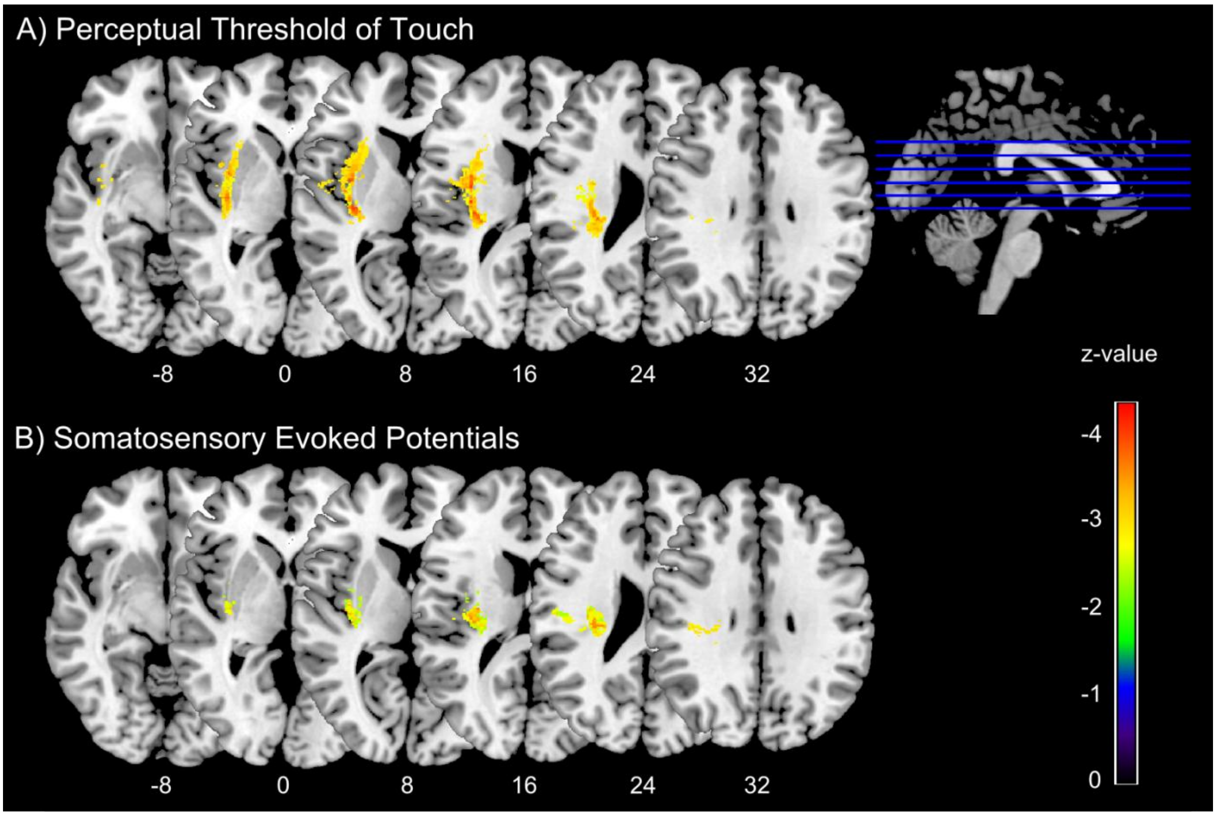

Figure 4 shows significant voxels from lesion-symptom mapping for A) the ***perceptual threshold of touch*** and B) ***somatosensory evoked potentials***, based on Liebermeister statistical test. Color scale indicates z-statistics. For test A). Results are corrected for multiple comparisons at a level of 1% FDR. For exploratory reasons in the SSEP analysis, results are corrected on a more liberal threshold (5% FDR), to account for the large amount of missing values. Statistical maps are overlaid on a T1-template in MNI space 1 × 1 × 1 mm³. MNI coordinates of each transverse section (z-axis) and a sagittal slice for visualization are given.

Discussion

In this voxel-based lesion-symptom mapping study we investigated which brain regions are important in the occurrence of exteroceptive and proprioceptive somatosensory deficits in the upper limb in the early phase post stroke. Although we observed a slight difference in extent and distribution of contributing voxels for deficits to the different somatosensory modalities, the analysis showed that lesions in two core brain regions were associated with both exteroceptive and proprioceptive deficits in the arm and hand post stroke: the parietal subcortical white matter near the postcentral region and the parietal operculum close to the insular cortex. The anatomical localization of the parietal subcortical cluster (MNI coordinate 29 / -25 / 25) corresponds to the sensory component of the superior thalamic radiation (sSTR) and thus represents the afferent sensory thalamocortical tract.[33] The second cluster in the parietal operculum (MNI coordinate 35 / -15 / 16) close to the dorsal insular cortex corresponds functionally to the secondary somatosensory cortex.[14]

Our results are well in line with VLSM-findings from Preusser and colleagues who identified the parietal operculum, together with the insular cortex, putamen, and subcortical connections reaching towards the prefrontal cortex to be causally involved in the perception of touch.[16] They highlighted the contribution of anterior parts of the parietal operculum (OP 4 and OP 3), which matches our findings including not only the parietal white matter but also parts of the insula to be related to light touch processing. Our peak cluster at MNI coordinate 35 / -15 / 16 is situated in the border zone of the second and third region of the parietal operculum (OP 2, maximum probability at 36 / -24 / 23; OP 3, maximum probability at 42 / -15 / 23), and to a lesser extent in the fourth region (OP 4, maximum probability at 60 / -12 / 19).[34] In contrast to the study of Preusser and colleagues who included a young cohort (mean age 46) of patients in the chronic stage of stroke (12 to 16 months after onset), we investigated both multiple exteroceptive and proprioceptive deficits in the acute stroke phase. Our results for pressure, pinprick, and proprioception showed similar involvement of the parietal white matter and the insulo-opercular cortex, however the amount of frontal insular voxels was less pronounced for proprioception. Thus, our study adds to the current knowledge that these brain areas are not only involved in the perception of touch, but are also important in the perception of pressure, pinprick and movement sense, especially in the early phase post stroke. While there were small differences in the extent and distribution of contributing voxels between the different somatosensory deficits, the overall pattern of lesion-deficit inference was similar. Therefore, a novel finding of this study is that different somatosensory modalities are affected by stroke lesions in the same brain areas. We further are the first to confirm results from clinical somatosensory assessments by quantitative measurements of exteroception and proprioception through recordings of the perceptual threshold of touch and somatosensory evoked potentials, respectively.

Our findings from probabilistic fiber tracking in healthy age-matched controls support that the two core brain regions identified by the VLSM analysis, in which lesions lead to both exteroceptive and proprioceptive deficits, have different projections to somatosensory-processing areas within the CNS. Both of the pathways seem to be involved in multimodal somatosensory processing. First, the parietal subcortical white matter cluster is in close relationship with the sensory component of the superior thalamic radiation (sSTR). Indeed, it showed strong connections to projection fibers from the dorsal brain stem through the dorsal internal capsule and thalamus up to the primary somatosensory cortex (postcentral gyrus). The relationship between post-stroke somatosensory ability and structural integrity of the sSTR has been determined previously.[33] Additionally to this projection, a frontal associative connection was found along the external capsule. This tract is very close to the ventral pathway described by Preusser and colleagues. Furthermore, a cerebellar pathway diverging from the main tract was found, usually containing sensory spinocerebellar fibers.[35] Second, the structural connectivity of the parietal opercular region revealed an association pathway between the parietal operculum, the insular cortex, the thalamus and the subcortical parietal white matter below the postcentral gyrus. This pathway contains sensory fibers from thalamus to the secondary somatosensory cortex reaching to the insular cortex as well as associative fibers between primary and secondary somatosensory cortex. Structural connections from ventroposterior lateral and inferior thalamic nuclei to secondary somatosensory cortex have been described previously.[15,36] Furthermore, strong structural and functional connectivity between S2 and posterior insular cortex has been reported.[37]

The insular cortex, anatomically located between the temporal, the frontal, and the parietal lobe, is considered to be a multimodal sensory integrative area.[38] The anterior and the posterior part of the insular cortex seem to have different functions. The anterior insular cortex plays a role in processing visceral sensation, the so called interoception[39] and in cognitive-affective aspects of pain perception.[40] The anterior part is further linked to body awareness[41] and has been even referred to as a neural correlate of consciousness.[42] In contrast, the dorsal insular cortex might represent a somatosensory association area,[43] being involved in processing of different exteroceptive functions. There is emerging evidence that the dorsal insular cortex is specifically involved in the perception of pain[44,45] and in the magnitude of perceived pain.[46] Abnormal pain thresholds are reported in patients with stroke lesion in the posterior insular cortex.[47] Mazolla and colleagues showed that there is a somatotopic organization in the human operculo-insular cortex with diverse activation patterns in response to different somatosensory stimuli.[38] In a small sample of patients with insular strokes, Baier and colleagues demonstrated by VLSM that insular stroke lesions are associated with impaired temperature perception.[17] In our study, we could demonstrate an expanded function of the posterior insular cortex, which was significantly associated to deficits in light touch, pressure, pinprick, and proprioception, underpinning the multimodal integrative function of the insula. Thereby our findings support the involvement of the dorsal insular cortex in processing of exteroception and proprioception, in contrast to the anterior insular cortex which has been previously referred to as being important for interoception.[39]

A few limitations of our study need to be addressed. First, to increase the generalizability of this study, we did not exclude patients with visuo-spatial neglect. Neglect is the inability to detect and respond to stimuli occurring in the hemi-space contralateral to a brain lesion, most commonly after right-hemisphere stroke.[48] In the present study, the number of patients with neglect was too small to draw conclusions about the correlation of neglect, somatosensory deficits and the corresponding brain regions that were affected. However, it is commonly alleged that brain regions important in somatosensory processing are in close proximity to brain regions responsible for neglect. Lesions affecting the superior and middle temporal gyrus, the temporo-parietal junction, the intraparietal sulcus and the insular cortex were found to be associated with spatial neglect. Also, the basal ganglia, especially putamen and caudate nucleus, the thalamus, and paraventricular white matter structures underlying the inferior parietal cortex were associated with neglect.[49-51] Therefore, neglect might have interfered with the somatosensory assessment due to the attention deficit. However, we also recruited patients with visuo-spatial neglect who did not have any somatosensory deficit, which supports the notion that somatosensory function in patients with visuo-spatial neglect can be tested. Furthermore, it is reassuring that our results are well in line with VLSM-findings from Preusser and colleagues[16] who excluded patients with visuo-spatial neglect in their study. Second, to increase statistical power of identifying lesion patterns, all lesion maps were flipped onto the right hemisphere. Therefore, hemisphere-specific information could not be studied, but we also did not have any hypothesis on lateralized processing of somatosensation. In our sample there was a bias regarding the side of the affected hemisphere that lead to more patients having a right hemisphere lesion. This was due to the fact that patients with left hemisphere stroke are more likely to have severe aphasia, which were excluded from the study. Furthermore, in the VLSM statistics, only voxels that were lesioned in at least ten patients could be investigated. Therefore, voxels tested in this analysis did not include some important brain regions for somatosensory processing such as the brainstem, thalamus and primary somatosensory cortex. Since the patients had stroke lesions, a selection bias towards brain lesions that correlate with vascular territories cannot be ruled out. Lastly, probabilistic tractography offers the advantage of modelling multiple fiber orientations to detect a range of subordinate pathways missed by deterministic fiber tracking. However, normalization of tractography to remove false-positive results is not standardized and remains arbitrary to some extent and has been discussed as a potential limitation previously.[31]

In summary, this VLSM study provides evidence that the sensory component of the superior thalamocortical radiation towards the postcentral gyrus is one of the most vulnerable brain regions to cause somatosensory deficits if lesioned by stroke. Furthermore, we endorse previous findings on the importance of the parietal operculum and insular cortex to somatosensory processing. The novel aspect of the present study is the combination of both voxel-based lesion-symptom mapping and probabilistic fiber tracking to investigate the relationship between different somatosensory deficits, measured with both standardized clinical assessment and more objective measures, and the underlying structural brain regions in a representative sample of patients with acute stroke. We found that similar lesion patterns are associated with multiple deficits in different somatosensory modalities in the upper limb. Future research should address the longitudinal somatosensory assessment with respect to lesion-symptom associations and the clinical question, to which extent somatosensory deficits can be regained during rehabilitation according to lesion localization.

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Author contributions

S.M. and S.S.K. contributed equally to this work.

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GENERAL DISCUSSION

The first part of this general discussion will summarize the main findings of this doctoral project, in relation to the specific objectives and research questions that were proposed. In the second part, critical reflections on the different studies of this doctoral project will be discussed and recommendations for future research will be presented. Third, considerations for physical therapy practice will be offered, and finally, an overall summary will be provided to conclude this general discussion.

1. Summary of main findings

This doctoral project aimed to provide insights into recovery post stroke with a focus on somatosensory dysfunction in the upper limb post stroke. Several specific objectives and research questions were addressed throughout the different chapters of this doctoral thesis.

In **Chapter 1**, the objective was to investigate the long-term time course of motor and functional recovery post stroke, and to explore which patient characteristics influence long-term motor recovery. These research aims were addressed in a European multicentre study. A longitudinal observational cohort study was performed in which 532 patients with stroke were included. Patients were assessed on admission to the rehabilitation centre, at two and six months and at five years post stroke using the Barthel Index (BI) and Rivermead Motor Assessment Gross Function (RMA-GF), Leg and Trunk function (RMA-LT), and Arm function (RMA-A). Long-term motor and functional recovery between admission to a rehabilitation centre and five years post stroke was analysed using linear mixed models, and the influence of age, gender, stroke severity and stroke pathogenesis on long-term outcome was evaluated. The results revealed a significant increase of 13-19% in mean BI, RMA-GF, RMA-LT, and RMA-A scores between admission and two months, and a mean increase of 6-9% between two and six months after stroke. Between six months and five years after stroke, a deterioration of 5-10% in mean functional and motor scores was found. Interestingly, this study showed that the mean scores of the estimates at two months and at five years after stroke showed no statistical and no clinical difference.

Increasing age and increasing stroke severity negatively affected outcome, and patients with intracerebral haemorrhage showed significant better arm function compared to patients with cerebral infarction during the entire study period. Although no individual prediction can be specified for long-term outcome based on this study, our results suggest that outcome at two months post stroke is on average equal to outcome at five years post stroke.

- Functional and motor outcome at five years after stroke rehabilitation is equivalent to functional and motor performance at 2 months after stroke.
- Increasing age and increasing stroke severity negatively affects long-term outcome.

In **Chapter 2**, the objective was to give an overview of the existing evidence on the association between somatosensory deficits in the arm and hand and upper limb impairments, activity and participation problems post stroke. A systematic review of the available literature until July 2013 was performed regarding the association between somatosensory impairments in the upper limb and outcome after stroke, within the different domains of the ICF model, namely body function, activity and participation. Six articles met all inclusion criteria. Large variation in results was found due to heterogeneity of studies. More specifically, at the level of body function, it was shown that two-point discrimination, somatosensory evoked potentials and the combination of light touch and proprioception were significantly related to motor impairments in the upper limb. However, only a small amount of the variance (R^2=0.01-0.08) in motor impairments could be explained by the somatosensory impairments. At the level of activities, proprioceptive impairments were shown to have predictive value in functional movement of the upper limb. Finally, at the level of participation, proprioception was significantly correlated with the perceived level of physical activity and social isolation and the combination of light touch and proprioception impairment was shown to be significantly related to restrictions during activities of daily living, with again only a small amount of the variance (R^2=0.03-0.06) being explained by the somatosensory variables. Despite the large variability in results, this systematic review showed that several somatosensory deficits are related to upper limb motor and functional performance after stroke.

- A systematic review of the available literature reveals that several somatosensory deficits were shown to be related to upper limb motor and functional performance after stroke, albeit explaining a small amount of the variance.

In **chapter 3**, the objectives were to map the prevalence and distribution of different somatosensory deficits in the upper limb, and to investigate whether visuo-spatial neglect is a confounding factor; and secondly to determine the association between several somatosensory impairments and motor impairment and activity limitations, both in patients with and without visuo-spatial neglect in the sub-acute phase post stroke. A cross-sectional observational study was performed, in which 122 patients with stroke were included, all within the first six months post stroke. Exteroceptive somatosensation included the measures of light touch, pressure and pinprick (of the Erasmus modified Nottingham sensory assessment, Em-NSA), and the perceptual threshold of touch (PTT). Proprioceptive somatosensation was assessed using the thumb finding test (TFT) and the proprioception subscale of the Em-NSA. Finally, higher cortical somatosensation comprised of sharp-dull discrimination, stereognosis and two-point discrimination. Screening for visuo-spatial neglect was performed using the star cancellation test. This study showed that upper limb somatosensory impairments are common in patients in the sub-acute phase post stroke, with prevalence rates ranging from 21-37% for exteroceptive impairments, from 23-54% for proprioceptive impairments and from 43-50% for higher cortical somatosensory deficits, with PTT, the TFT and stereognosis revealing the highest frequencies in exteroceptive, proprioceptive and higher cortical somatosensory deficits, respectively. When comparing patients with and without visuo-spatial neglect, we found that patients with visuo-spatial neglect have more often and more combined and significantly more severe somatosensory deficits in all the different somatosensory outcome measures compared to patients without neglect.

Furthermore, the association between different somatosensory impairments and motor impairment and activity limitations was investigated. Upper limb motor assessment comprised the Fugl-Meyer assessment, motricity index and action research arm test, whereas activity limitation was assessed using the adult-assisting hand assessment stroke. Our results showed that in patients with neglect, consistently stronger associations exist (r=0.44-0.78) between somatosensory impairments and both motor impairments and activity limitations, compared to patients without neglect (r=0.08-0.59). On the other hand, the correlation between PTT and all three motor outcomes and activity limitations, was comparable for patients with neglect (r=0.46-0.55) and without neglect (r=0.55-0.59).

Finally, the strongest association between somatosensory and motor impairment was found for stereognosis, both in patients with (r=0.72-0.78) and without neglect (r=0.40-0.51). Overall, this study showed that somatosensory deficits are common in the sub-acute phase post stroke, and that the presence of visuo-spatial neglect is associated with the presence and severity of different somatosensory and motor deficits.

- Upper limb somatosensory impairments are common in patients in the sub-acute phase post stroke, with prevalence rates ranging from 21% to 54%.
- Patients with visuo-spatial neglect have more combined and more severe somatosensory deficits compared to patients without neglect.
- In patients with neglect, consistently stronger associations exist between somatosensory impairments and motor impairments and activity limitations, compared to patients without neglect.

In **chapter 4**, the objectives were to map the change in prevalence and distribution of different somatosensory deficits in the upper limb measured in the acute and chronic phase; and secondly to determine the association between somatosensory impairments and motor impairment and activity limitations, both in the acute and chronic phase post stroke. A longitudinal observational study was performed, in which 32 patients with stroke were included. Patients were assessed four to seven days post stroke, and again at six months. The prevalence and distribution of different somatosensory impairments, including exteroceptive, proprioceptive and higher cortical somatosensory deficits, were mapped at both time points, using the same somatosensory outcome measures as reported in chapter 3. This study showed that somatosensory impairments are common in the acute phase post stroke, with 41-50% experiencing exteroceptive impairments, 44-63% having proprioceptive impairments and 50-63% suffering higher cortical somatosensory impairments. Overall, the distribution analysis showed that 78% experiences one or more somatosensory impairment within the first week, with mostly mixed exteroceptive, proprioceptive and higher cortical somatosensory deficits. Although many of the patients recover from different somatosensory impairments, still more than half of the patients have remaining deficits at six months. At six months, the prevalence of exteroceptive impairments dropped to 3-22%, with PTT revealing the highest frequency, whereas higher cortical somatosensory impairments were still present in 22-28% of the patients. Remarkably, the prevalence of proprioceptive impairments decreased to 3% when using the Em-NSA, whereas still 50% of participants had a position sense deficit assessed by the TFT.

Furthermore, the association between different somatosensory impairments and motor impairment within the first week, and with motor impairment and activity limitations at six months was investigated. Upper limb motor assessment comprised the Fugl-Meyer assessment, motricity index and action research arm test, whereas activity limitation was assessed using the adult-assisting hand assessment stroke, the ABILHAND questionnaire and the hand function subscale of the stroke impact scale. In the acute phase, there was a very low association (r=0.03 – 0.20) with motor impairment, whereas at six months, low to moderate correlations were found for the association between motor impairments and different exteroceptive, proprioceptive and higher cortical somatosensory impairments. For exteroceptive impairments, PTT showed moderate correlations with all motor impairment measures (r=-0.60 to -0.66) and proprioceptive impairments measured with both the TFT, as well as the movement sense scale of the Em-NSA showed low correlations (r=0.26 – 0.39) with motor impairments. Finally, at the level of higher cortical somatosensory impairments, low to moderate correlations (r=0.37 – 0.56) were found for the link between motor function and stereognosis. Additionally, a similar pattern was found for the association between somatosensory impairment and activity limitations at six months. Therefore, a more severe somatosensory impairment was associated with more severe motor impairment and more restricted functional hand use. Although no conclusions can be drawn on causality, our results suggest that the impact of somatosensory deficits on upper limb motor and functional performance increases with time after stroke.

- Upper limb somatosensory impairments are common both in the acute and the chronic phase post stroke.
- In the acute phase, there is little association between somatosensory impairment and motor impairment, whereas at six months, different somatosensory impairments are related to motor impairments and activity limitations.

In **Chapter 5**, the objective was to investigate the relationship between stroke lesion location and the resulting somatosensory deficit in the upper limb in the acute phase post stroke. A cross-sectional observational study was performed, in which 38 patients with stroke were assessed four to seven days post stroke. The Em-NSA was used to clinically assess light touch, pressure, pinprick and proprioception. Furthermore, two quantitative outcome measures were used, namely PTT and somatosensory evoked potentials (SSEP). Besides the somatosensory assessment, either a 2D or 3D FLAIR MRI was acquired. Non-parametric voxel-based lesion-symptom mapping (VLSM) was performed to investigate the lesion contribution to different somatosensory deficits in the upper limb. The extent and distribution of significant voxels differed slightly between the four Em-NSA tests. The largest area of significant voxels was found for light touch deficits including the parietal white matter parts of the corona radiata inferior to the post- and precentral gyri, the parietal operculum, the insular cortex, and the external, dorsal internal, and extreme capsule. Significant voxels associated to a pressure deficit included similar regions as for light touch, but with lesser involvement of the frontal parts of the external and extreme capsule and the insular cortex. Maximal association was found in the parietal operculum and the parietal white matter of the corona radiata, inferior to the post- and precentral gyrus. Voxels associated with pinprick deficits were found in the parietal operculum as well as in the white matter inferior to the post- and precentral gyri. Finally, the test for proprioception deficit identified the smallest number of voxels, including the corona radiata inferior to the post- and precentral gyrus as well as small parts of the parietal opercular and the dorsal insular cortex. Our quantitative recordings confirmed findings from clinical assessments. Voxels with a significant association to all somatosensory deficits were clustered in two core brain regions: the central parietal white matter, also referred to as the sensory component of the superior thalamic radiation, and the parietal operculum close to the insular cortex, representing the secondary somatosensory cortex.

Additionally, structural connectivity of these two core brain areas was determined, using probabilistic fiber tracking based on diffusion tensor imaging data from a healthy age-matched sample (n=24). Probabilistic tracking connected the sensory component of the superior thalamic radiation to thalamus, internal capsule, brain stem, postcentral gyrus, cerebellum, and frontal pathways, while the secondary somatosensory cortex demonstrated structural connections to thalamus, insular and primary somatosensory cortex. These novel findings may form the basis for future brain imaging research, as the core brain regions for processing different somatosensory stimuli are defined.

- Voxel-based lesion-symptom mapping showed that lesions in two core brain areas are associated with different somatosensory impairments: the sensory component of the superior thalamic radiation and the secondary somatosensory cortex.

2. Critical reflections and recommendations for future research

In this general discussion, the most important critical reflections related to the different studies of the doctoral project will be discussed and starting from these reflections, recommendations for future research will be given.

The long-term follow-up study of the CERISE project **(chapter 1)** is the first large cohort study providing long-term outcome after stroke rehabilitation collected from different European centres. The study showed that functional and motor outcome at five years after stroke rehabilitation is equivalent to functional and motor performance at 2 months after stroke. However, a few considerations are needed when interpreting the results. First, recovery was shown up to 5 years after stroke, but time points between 6 months and 5 years were unavailable. As a consequence, we were not able to describe a complete long-term recovery pattern or to determine where improvement in motor or functional outcome ends and deterioration starts. Future studies should shorten the time intervals between measurements to provide further knowledge concerning the long-term recovery pattern. Secondly, this study provides little information on the duration, frequency, and content of long-term rehabilitation programs, as well as on the effectiveness of current models and therefore this remains a gap in the current knowledge. Future studies are needed to map the content and intensity of the treatment programs currently provided after inpatient rehabilitation. Furthermore, the effect of novel therapy approaches in the chronic phase post stroke need to be determined, in order to prevent deterioration in outcome long-term post stroke. Intermittent training, such as constraint-induced movement therapy,[1] or home-based self-directed therapy with technology support[2] may be a useful alternative to ongoing traditional therapy approaches in the chronic phase, both from a clinical and an economical perspective, to hopefully optimize long-term outcome after stroke.

The systematic review reported in **chapter 2** provided a detailed overview of the existing literature on the association between somatosensory impairments and outcome after stroke. Despite the large heterogeneity between studies, the review showed that different somatosensory impairments are related to motor and functional outcome in the upper limb. Though, two main restrictions are related to this systematic review**.** First, a pooling of results in a formal meta-analysis was precluded due to heterogeneity among included studies with regard to the study designs, somatosensory and outcome measures, and there was great variability in lengths of follow-up, data analysis, and presentation methods. Bias in setting and study participants needs consideration when indirectly comparing results across studies. Therefore, it was not possible to draw more detailed conclusions about the impact of different somatosensory modalities on outcome after stroke. For example, the question whether light touch impairment might have a higher predictive value compared with proprioceptive impairment in outcome after stroke could not be answered due to the lack of studies combining measures of somatosensory function in predicting outcome after stroke. Therefore, future high-quality and large-sample cohort studies should combine reliable and valid measures of different somatosensory modalities, to determine the relationship with motor and functional outcome with more accuracy. Second, it should be noted that quality appraisal is a concern with this type of systematic review.[3] Because of the lack of a gold standard for assessing quality of observational studies, we modified the methodological quality assessment of the Downs and Black quality scale.[4] This scale was originally designed to assess the methodological quality of health care interventions. Different questions of this quality appraisal instrument were therefore not applicable due to the nature of the observational study designs included in this review. The Downs and Black checklist comprises 5 major categories: reporting, external validity, internal validity – bias, internal validity – selection bias and power. This scale was chosen as this was recommended in a systematic review[5] rating instruments for assessing quality of observational studies and the Cochrane Collaboration has a chapter in their handbook[6] for assessing quality in non-randomized studies that recommends the same instrument. Alternative checklists are available in the literature such as the Newcastle-Ottawa Scale (NOS) or the Scottish Intercollegiate Guidelines Network (SIGN), albeit with recognised limitations.[5] Another checklist is available through the equator network website: the checklist for strengthening the reporting of observational studies in epidemiology (STROBE).[7] However, caution is required as this list provides a reporting checklist, and is not developed to consider quality. Therefore, further efforts are needed on the development of quality assessment tools for observational studies, possibly by refining the existing quality appraisal tools.

Our systematic review highlighted the need to use reliable and valid measures of somatosensory functions in research. During the study selection process, a large number of studies were excluded from the systematic review based on the absence of psychometric data of the somatosensory measure. Unfortunately, all efforts invested when conducting these studies are nullified when assessments of poor psychometric quality are used. A systematic review by Connell and Tyson[8] summarized the available evidence on the clinical utility and psychometric properties of outcome measures of somatosensation in neurological conditions. The psychometric properties that were assessed are concurrent validity, test-retest and inter-rater reliability and the ability to detect change. This review showed that future research should concentrate on further examining validity, the ability to detect change and the reliability of the assessment methods. Reliability can be improved by careful standardization and detailed operating instructions. Although none of the assessment methods fulfilled all of the psychometric criteria, the Erasmus version of the Nottingham sensory assessment showed the best balance between clinical utility and psychometric properties. Therefore, this clinical assessment scale was further used in chapter 3, 4 and 5 to map impairments in somatosensory functioning.

Both the cross-sectional study reported in **chapter 3** and the longitudinal study reported in **chapter 4** investigated the prevalence and distribution of different somatosensory deficits in the different phases post stroke. The strength of the studies is that we included a combination of reliable and valid assessment methods to map impairments in different somatosensory modalities of exteroceptive, proprioceptive and higher cortical functioning in a large cohort of stroke patients. Furthermore, besides the pure clinical assessment methods, we used a more objective measure to assess the exteroceptive function, namely the perceptual threshold of touch (PTT).[9] Still, an important consideration relates to the broad time window for inclusion of patients post stroke in the cross-sectional study. Patients were assessed within the first six months after stroke, without further limiting the time window. Therefore, patients were assessed between 12 and 197 days post stroke, with only 8% of the patients between 12 days and one month, 53% between one and three months, and 39% between three and six months after stroke. Furthermore, our longitudinal study has only two time points, namely within the first week and at six months post stroke. Future studies should include more fixed time points between the first week and six months for the assessment of somatosensory function, to map recovery patterns in more detail in a larger cohort of patients post stroke. Up to now, only one study[10] investigated somatosensory recovery in 70 stroke survivors from admission to a rehabilitation unit up to six months post stroke. In between, patients were also assessed at two and four months post stroke. The somatosensory recovery showed a similar pattern to the widely known motor recovery,[11] with most recovery in the first weeks after stroke, and the recovery slope reaching a plateau between three and six months. Therefore, future studies should look at the influence of time on recovery of different somatosensory impairments from the acute phase up to six months post stroke.

In addition, our studies reported in **chapter 3 and 4** provided a full overview of the association between different somatosensory impairments in the upper limb and outcome at the three levels of the ICF-model:[12] body function, activities and participation, in the different phases post stroke. Our longitudinal study showed that in the acute phase, there was only little association, though, our results suggest that the impact of somatosensory deficits on upper limb motor and functional performance increases with time after stroke. However, due to the restricted sample size of 32 patients with stroke in this study, a multivariate prediction analysis was not conducted. Consequently, it is recommended to investigate the predictive value of different somatosensory deficits in the acute phase on outcome at six months post stroke in a larger cohort study. The very low association between somatosensory and motor impairment in the acute phase poste stroke can most likely be attributed to the large amount of patients with both very poor motor and somatosensory function in the acute phase, probably reflecting large brain lesion and more severe strokes. The increasing strength of the association between somatosensory and motor impairments over time might therefore be associated with recovery of both functions over time, but might also be a reflection of the importance of somatosensory deficits in the development of learned non-use. Learned non-use is a phenomenon in which the patient does not use the hemiplegic upper limb spontaneously during activities of daily living (IFC – activity level), but the patient is able to use the upper limb, as the motor capacity is intact (ICF – impairment level).[13] Learned non-use is often a result of unsuccessful attempts when executing motor tasks (incoordination, dropping objects) when using the hemiplegic upper limb, which lead to decreased motivation to use the hemiplegic arm and hand in daily activities. This will further lead to a vicious circle: the lesser the patient moves with that hemiplegic side, the smaller the cortical representation in the brain, the more effort is needed to perform the movement. Additionally, compensatory behavior patterns are reinforced, in which the patient is capable of performing motor tasks successfully, without the use of the hemiplegic side. This phenomenon was first observed in basic research on monkeys, in which somatosensory function was surgically abolished (deafferentiation) in one of the forelimbs, without destruction of the motor innervation. This research showed that the deafferentiated forelimb was no longer used in daily activities, even though they possessed sufficient motor function. The abolition of somatosensory feedback which drives motor function, resulted in incoordination and dropping of objects. Compensation mechanisms became more efficient, and this then led to a learned non-use of the affected forelimb. In humans, detrimental effects of somatosensory impairments on motor function have been documented. A number of authors[13-15] reported a negative impact on spontaneous hand use, often despite no apparent loss of motor function. It has been suggested that learned non-use occurs as a consequence of somatosensory loss and that this disuse may lead to further deterioration of motor function.[14] Future research is necessary to gain further insights in the concept of learned non-use, and to examine whether these patients with learned non-use have more somatosensory impairments compared to patients with similar motor function, who do use the arm in activities of daily living.

The main critical consideration of the cross-sectional study reported in **chapter 3,** relates to the assessment of visuo-spatial neglect. Visuo-spatial neglect was only considered as a co-factor and therefore measured with solely the star cancellation test (SCT).[16] Although this test is widely used both in clinical practice as well as for research purposes, this might be seen as limited in order to assess the complex phenomenon of neglect. However, the SCT was chosen as it showed to be the most sensitive paper-and-pencil measure of visuo-spatial neglect, with high interrater reliability.[17,18] Nevertheless, it should also be acknowledged that neglect might interfere with the somatosensory assessment due to the attention deficit. Therefore, some cases might have been erroneously classified as having somatosensory impairments when they in fact had only an attention deficit. Though, neglect was assessed using the SCT, a test for visuo-spatial extra-personal neglect, which is distinct from tactile personal neglect, of which the latter might more strongly interfere with somatosensory testing.[19] Furthermore, our results showed that there are patients with visuo-spatial neglect without any somatosensory deficit, which shows that you can assess somatosensory function in patients with visuo-spatial neglect. Future research is necessary to replicate our findings that patients with neglect have more combined and more severe somatosensory impairments with a more extended test battery for visuo-spatial neglect, such as the behavioural inattention test (BIT),[20] as well as outcome measures for personal, tactile neglect such as the comb and razor test.[21] Future studies can then look further into detail about the relation between different subtypes of neglect and somatosensory impairments. We further acknowledge that we were not able to investigate the influence of neglect on sensorimotor recovery in the longitudinal study, reported in **chapter 4**, due to the small group of patients with neglect (n=5) in this study.

Finally, patients with cognitive impairments were not included in the studies reported in **chapter 3, 4 and 5**. The screening for cognitive impairment was performed by a subjective evaluation of the assessor without the use of standardised assessment methods. Although we do believe that the subjective assessment was adequate for screening of cognitive impairments to determine the feasibility of conducting the study protocol, we encourage future researchers to screen for cognitive impairments in a more standardised way, in order to assess whether cognition is an important co-factor in sensorimotor recovery after stroke. Additionally, we only included patients with a motor and or somatosensory impairment in the upper limb post stroke. Therefore, caution is needed when generalizing the results to the whole stroke population.

In the cross-sectional study reported in **chapter 5**, a combination of both voxel-based lesion-symptom mapping and probabilistic fiber tracking was used to investigate the relationship between different somatosensory deficits and the underlying structural brain regions. These techniques enable us to investigate the structure-function relationship in more detail. Though, a few limitations of this study need to be further addressed. First, we evaluated the contribution of specific brain lesions to the occurrence of exteroceptive and proprioceptive somatosensory impairments. As the group of patients with pure higher cortical somatosensory impairments was too small, we were not able to address the question which lesions contributed to these specific higher cortical impairments. Therefore, new large studies are needed to look at this symptom-lesion relationship, including a larger number of patients with higher cortical somatosensory impairments. Secondly, this was a cross-sectional study assessing patients within the first week post stroke. Future research should evaluate lesion-symptom associations in a longitudinal manner to evaluate to which extent somatosensory deficits can be regained during rehabilitation according to lesion localization. Third, we did not exclude patients with visuo-spatial neglect. The number of patients with neglect was too small to draw conclusions about the correlation of brain regions that were affected and the occurrence of neglect and somatosensory deficits. However, it is well known that brain regions responsible for neglect are in close proximity to brain regions important in somatosensory processing. Spatial neglect was in previous studies associated with lesions affecting the temporo-parietal junction, the intraparietal sulcus and the insular cortex. Furthermore, the thalamus, basal ganglia, and paraventricular structures in the white matter, underlying the inferior parietal cortex were associated with neglect.[22-24] Future studies should explore more in detail the shared anatomical correlates of both neglect and somatosensory deficits. Fourth, for the voxel-based lesion symptom mapping statistics, only voxels that were lesioned in at least ten patients could be investigated. Therefore, voxels tested in this analysis did not include some important brain regions for somatosensory processing such as the brainstem, thalamus and primary somatosensory cortex. As a consequence, caution is required when generalizing the results, and validation of our findings is necessary in another cohort.

Finally, as the aim of this study was to look at the structure-function relationship based on structural MRI images, information from other structural or functional brain imaging techniques is not addressed in this study. Therefore, further research is needed to look into the relationship between somatosensory impairments and structural and functional connectivity of the brain. Up to now, several studies evaluated activation patterns of brain areas post stroke in response to a somatosensory stimulus using functional MRI. In patients with chronic haemorrhagic stroke, activation of the primary sensorimotor and posterior parietal cortex was seen during light touch stimulation. This activity was negatively associated with the degree of tactile sensory deficit.[25] In another study on patients with sub-acute subcortical stroke, texture discrimination sense during functional MRI was negatively correlated with brain activation in the ipsilesional primary and secondary somatosensory cortex, the contralesional thalamus and frontal attention regions, whereas in patients with cortical stroke, no significant correlated activity was found.[26] Additionally, a study of Van de Winckel and colleagues[27] showed that both in patients with subcortical stroke and healthy elderly, shape discrimination based on passive finger movements, resulted in activation of the anterior intraparietal sulcus and premotor area, whereas length discrimination elicited a more medially located parietal activation.[27] There is a paucity of studies using diffusion tensor imaging (DTI) or resting-state functional MRI (rs-fMRI) to assess the relationship with somatosensory impairments post stroke. These techniques might advance our understanding about the neural correlates of different somatosensory functions. Besides a cross-sectional assessment of these relationships, future longitudinal studies are needed to evaluate to which extent behavioral changes in somatosensory functioning is reflected in changes in the structural or functional connectivity of important brain regions. Despite these limitations, the novel aspect of the present study is the combination of both voxel-based lesion-symptom mapping and probabilistic fiber tracking to investigate the relationship between different somatosensory deficits, measured with both standardized clinical assessment and quantitative measures, and the underlying structural brain regions in a sample of patients with acute stroke.

In summary, based on the results of this doctoral thesis, **recommendations for future research include: (1)** to map recovery from the acute phase up to several years post stroke in large international cohort studies, with short time intervals between measurements, using a core data set of standardized outcome measures at fixed time points; **(2)** to study the content and intensity of the current treatment after inpatient rehabilitation and to evaluate the effect of novel therapy approaches in the chronic phase post stroke, in order to prevent deterioration in outcome long-term post stroke; **(3)** to develop quality appraisal tools for observational studies to be used in future systematic reviews, possibly by refining existing quality assessment tools; **(4)** to further examine reliability, validity and the ability to detect change of the outcome measures for somatosensory impairments post stroke. Reliability might be improved by careful standardization and detailed operating instructions; **(5)** to look further into detail about the relation between different subtypes of neglect and somatosensory and motor impairments; **(6)** to examine the influence of time on recovery of sensorimotor function, in combination with recovery of visuo-spatial neglect; **(7)** to investigate the predictive value of different somatosensory deficits in the acute phase on outcome at six months post stroke in a larger cohort study; **(8)** to map the recovery of different somatosensory impairments from the acute phase up to six months post stroke with more fixed time points between the acute and chronic phase; **(9)** to study somatosensory symptoms and brain lesion relationship in larger longitudinal studies, including a large amount of patients with exteroceptive, proprioceptive and higher cortical somatosensory impairments; **(10)** to explore directly the shared anatomical correlates of both neglect and somatosensory deficits; and **(11)** to examine the relationship between somatosensory impairments and structural and functional connectivity in the brain using advanced structural and functional brain imaging techniques, such as DTI or rs-fMRI.

3. Considerations for physical therapy practice

The findings of this doctoral project may have several implications for physical therapy practice. The particular merit of the present thesis is the increased understanding of somatosensory impairments in the upper limb post stroke, especially mapping the prevalence and distribution of impairments in different somatosensory modalities, as well as exploring the importance of these impairments in motor and functional outcome. Future research is needed to justify the proposed clinical implications. Nevertheless, the present discussion allows speculation on how these clinical implications can be elaborated. As shown below, specific take-home messages are formulated in terms of the evaluation and treatment of somatosensory impairments post stroke.

3.1. Assessment of somatosensory impairments

The importance of assessing somatosensory impairments as an essential part of the clinical assessment process is recognized by both patients and health care personnel.[28] Therefore, a first recommendation for practice is the use of reliable and valid measurement instruments to assess somatosensory impairments post stroke. A recent study of Pumpa et al.[29] showed that most therapists working in stroke rehabilitation, routinely assess somatosensory impairments, but with the majority not using standardised measures. Despite published evidence by Connell and Tyson,[8] which offers a guideline for using reliable, valid, and clinically useful measures of somatosensation in clinical practice, an evidence-practice gap was identified.[29] Although the measurement of all somatosensory modalities looks impracticable and difficult to justify in the clinical setting in patients with stroke, we do recommend assessing patients from the acute phase after stroke along the rehabilitation process with a core set of outcome measures to accurately monitor progress in recovery in the different somatosensory modalities.

Based on our findings, we propose to use a set of three screening outcome measures, one for each of the following somatosensory categories, namely exteroceptive, proprioceptive and higher cortical somatosensory functioning. The proposed screening set includes the perceptual threshold of touch (PTT)[9] for exteroceptive function, the thumb finding test (TFT)[30] for proprioceptive function and the stereognosis assessment[31] for higher cortical somatosensory function. The reason for the selection of these three outcome measures is twofold, based on the results of studies reported in chapter 3 and 4. First, these outcome measures revealed the highest frequency of exteroceptive, proprioceptive and higher cortical dysfunction. Therefore, these measurements are most likely to capture small somatosensory deficits. Second, these outcome measures showed the strongest association with motor function, in the sub-acute and chronic phase post stroke. If these screening tools detect an impairment in exteroceptive, proprioceptive or higher cortical function, we do recommend using the full core set of outcome measures that were used in our studies, as displayed below in figure 1, to examine in detail impairments in the different somatosensory modalities.

Figure 1. Recommendations for the assessment of somatosensory impairments in the upper limb after stroke

Screening set		**Core set**
Exteroceptive function		
Perceptual threshold of touch		
Score > norm-value?	→	Erasmus modified Nottingham Sensory Assessment
		Light touch
		Pressure
		Pinprick
Proprioceptive function		
Thumb finding test		
Score > 0 ?	→	Erasmus modified Nottingham Sensory Assessment
		Movement sense
Higher cortical somatosensory function		
Stereognosis		
Score < 19 ?	→	Erasmus modified Nottingham Sensory Assessment
		Sharp-dull discrimination
		Two-point discrimination

However, when considering this recommendation for clinical practice, a few important contemplations are warranted concerning different measurement properties of the recommended somatosensory outcome measures. Recently, the COSMIN group[32] developed a checklist for assessing the methodological quality of studies on measurement properties of health-related outcomes, for selecting the right measurement instruments in clinical practice or at the start of a new study, or for identifying the need for further research on measurement properties. This scale is therefore helpful for both clinicians and researchers.[32]

A first consideration relates to the selection of scales recommended for the screening set. These were primarily selected based on the detection of the highest frequency of exteroceptive, proprioceptive and higher cortical dysfunction. However, due to the absence of a gold standard for somatosensory assessments, we are unable to assess the criterion validity. A gold standard would make it able to determine sensitivity and specificity of the measurement instrument when dealing with dichotomous scores.[32] Therefore, up to now, we cannot ascertain that the detection of high frequencies in deficits when using the PTT, TFT or stereognosis assessment, is reflecting high sensitivity (all deficits are true somatosensory deficits) of the measurement and whether the specificity of these measurement instruments is high (few false positives). Future research should concentrate on the development of gold standard tools to assess somatosensation. For proprioceptive deficits, this might be performed through robotic devices or quantitative motion tracking systems. Different studies[33-37] showed the advantages of these quantitative methods for the evaluation of arm position or movement matching tasks in patients with stroke. These devices are shown to be reliable, valid and highly sensitive in capturing small proprioceptive deficits during the tracking of different variables such as movement direction, speed, magnitude or latencies.[33-37] Future research should combine both clinical measures and robotic devices in order to assess criterion validity of the clinical scales for use in clinical practice and for research purposes. Another more quantitative measure of somatosensory function is the assessment of somatosensory evoked potentials.[38] It measures the transmission of sensory signals from the peripheral nerve at the wrist through the dorsal system up to the cerebral cortex. Although again less clinically utile, this measurement has the advantage that it can be performed in patients with cognitive, attention or communication deficits, as no cooperation from the patient is needed.

Secondly, we assessed recovery of somatosensory impairments over time, using different outcome measures. Important to notice is that only for the PTT, standard error of measurement (SEM) is provided in literature, reflecting the measurement error. A change of >1mA was considered as true change in PTT function, beyond the measurement error.[9] Neither for the EM-NSA, TFT, two-point discrimination or the stereognosis assessment, the measurement error was defined, therefore interpretation of changes in scores over time is limited. Future research is needed to assess the measurement error of the different measurement instruments. Third, we acknowledge that attention deficits, such as visuo-spatial neglect, might have interfered with the somatosensory assessment. Therefore, we cannot ascertain that the scores on the different somatosensory outcome measures are only reflecting true somatosensory impairment. However, we also recruited patients with visuo-spatial neglect who did not have any somatosensory deficit, which supports the notion that somatosensory function in patients with visuo-spatial neglect can be tested. Fourth, the differences in prevalence detected by the different measures might also be attributable to true differences in modalities, although all reflecting exteroception or proprioception. For example, it is plausible that position sense measured with the TFT is truly different from movement sense measured with the Em-NSA, although both are forms of proprioception. The same might be true for the light touch measure of the Em-NSA and the PTT. Although both the clinical assessment of light touch, using a cotton wool, and PTT stimulate the same receptors and scores were significantly correlated in our study (r=-0.634), the perceived stimulus is different as in PTT an electrical current is felt.

A final consideration relates to sensory decline in healthy ageing. Previous studies showed that cutaneous sensation deteriorate significantly with age.[39-41] Bowden and McNulty[39] assessed perceptual thresholds in the hands in 70 subjects ranging from 20 to 88 years old, using Semmes-Weinstein monofilaments, two-point discrimination and texture discrimination. Both the cutaneous threshold determined with the monofilaments as well as two-point discrimination, deteriorated significantly with age. Texture discrimination also decreased with age, although not significant.[39] In a study of Dunn et al.,[40] changes in somatosensation across the lifespan were measured. A total of 367 patients (age 3-85 years old) were tested for movement sense, position sense, texture discrimination and stereognosis, using different outcome measures. The study showed that older adults (>70 years old) were less accurate in movement sense and stereognosis, whereas no consistent changes were found for position sense and texture discrimination.[40] Finally, Dukelow et al.,[41] used the thumb finding test to assess position sense deficits in a group of 65 healthy elderly (median age 63 years old). In 5 subjects (8%), a score larger than 0 was found, indicating a position sense deficit.[41] Up to now, only for the PTT and two-point discrimination norm-values are determined and reported in the literature.[42,43] Normative values of the different other scales of healthy elderly need to be determined, in order to assess the influence of age-related changes on the performance of these tests, and to interpret the findings in stroke patients.

Despite these considerations and gaps in the current literature, we believe that it is important to provide recommendations for the assessment of somatosensory impairments, based on the current knowledge. The proposed set of outcome measures is clinically very utile, as the time to complete the test, the cost and the equipment needed is limited.[8] Furthermore, for the Em-NSA,[44] detailed structured guidelines are publically available (http://www.erasmusmc.nl/cs-fysiotherapie/beeld/4887961/h.emnsa) which increases standardisation. The only test that requires more specialised equipment is the PTT, namely a device that can produce high-frequency TENS.[9] In our studies a CEFAR Primo Pro (Cefar Medical AB, Sweden) was used, with a cost of approximately €200.

3.2. Treatment of somatosensory impairments

Up to now, results from somatosensory assessments have not been routinely used to set goals for treatment programs. Treatment of somatosensory deficits is warranted because it may also positively influence motor output.[45] A Cochrane review[46] performed in 2009 on interventions for sensory impairment in the upper limb post stroke showed that multiple interventions for upper limb sensory impairment after stroke are described but there is insufficient evidence to support or refute their effectiveness in improving sensory or motor impairment or functional hand use. Still, two small sample sized studies included in the review suggested preliminary evidence for the effects of some specific interventions, such as thermal stimulation and intermittent pneumatic compression for improving somatosensation after stroke.[46] Cambier et al.[47] evaluated the efficacy of intermittent pneumatic compression for treating sensory problems in the upper limb in a sample of 23 subacute to chronic stroke survivors. The experimental group (n=11) received intermittent pneumatic compression treatment through an inflatable pressure splint covering the whole arm (10 cycles of 3 minutes with a peak of 40 mmHg pressure). The control group (n=10) received a sham short-wave therapy on the hemiplegic shoulder. Both the experimental and control treatment was performed for 30 minutes each day, five days a week for a period of four weeks. Between-group differences in favor of the experimental group were reported for the restoration of exteroceptive and proprioceptive function after the end of the intervention, as assessed with the Nottingham sensory assessment, but not for motor function.[47] The study of Chen et al.,[48] aimed to investigate the effect of thermal stimulation in a group of 15 patients in the acute to subacute phase post stroke. Thermal stimulation on the hand was applied through monitored hot and cold packs for 15 and 30 seconds respectively. The patients were encouraged to actively move away from the stimulus after this time interval. One session of thermal stimulation was performed daily, including two alternate cycles of heating and cooling stimulation. This program was continued for six weeks with five sessions each week. Thermal stimulation significantly enhanced recovery of exteroceptive function, as assessed with the Semmes-Weinstein monofilaments, as well as recovery of motor function, measured using the Brunnstrom stages.[48]

Another promising result arises from a study by Carey et al.,[49] in which the effectiveness was shown of a perceptual-learning based sensory discrimination program (SENSe) on sensory discriminative ability in 50 patients in the chronic phase post stroke. A total of 10 interventions, of 60 minutes each, three times a week were given including texture discrimination, limb position sense and tactile object recognition training. The training included a wide variety of stimuli with graded progression and different forms of feedback. Improvements were maintained at six weeks and six months post intervention.[49] The effectiveness of the intervention for improving motor outcome or functional hand use needs further investigation, especially in the acute and subacute phase post stroke. Furthermore, cognitive sensory motor training therapy, also known as the Perfetti-concept,[50] might be a useful alternative for conventional therapy, although it might be more time-consuming and requires one-on-one training. The Perfetti concept focuses on sensory retraining, with particular emphasis on joint position sense. As patients progress through the proprioceptive training, they end with the 'assisted explorative movement' phase, in which they are asked to move the arm and hand over a stationary object and to sense the length, height, hardness or shape of the object, while blindfolded. A recent randomized controlled trial[50] investigated the effectiveness of the cognitive sensory motor training therapy to improve fine motor performance, gross motor dexterity and basic activities of daily living, however, there was no evidence for superiority in comparison with conventional occupational therapy. Nevertheless, for patients with very severe paresis in the upper limb, the Perfetti approach might be worthwhile, because statistically significant improvements were found in the Perfetti group in comparison with the conventional therapy group. Therefore, this method might be more suitable for treating patients with very severe arm and hand paresis and might have an important role in rehabilitation of severely affected patients.[50]

Furthermore, several studies reported positive effects of peripheral somatosensory nerve stimulation, in combination with task specific training for the upper limb in the chronic phase after stroke.[51,52] First, Kim et al.,[51] compared the efficacy of task-related training combined with transcutaneous electrical nerve stimulation (TENS) (n=15) with task-related training combined with a placebo stimulation (n=15) on recovery of upper limb motor function. The task-related training involved arm and hand tasks that were related to functional movements needed during daily living, and the training was conducted during a 30 minute session each day, five days a week for a period of four weeks. Additionally, after the task-related training, a 30 minute TENS stimulation was applied to the muscle belly of the triceps and wrist extensors, with an intensity of two to three times the sensory threshold inducting a visible muscle twitch. For the placebo group, the electrodes were attached at the same locations, but the stimulation was not applied. This study showed a beneficial effect of the combination of task-related training with TENS for improving motor function and dexterity and reducing spasticity when compared to task-related training combined with a placebo stimulation immediately after the intervention.[51] Recently, Fleming and colleagues[52] showed that somatosensory stimulation of all three peripheral nerves at the forearm for two hours (intensity of three times the sensory threshold), followed by 30 minutes of task specific training has a favourable effect on upper limb function, compared to a sham stimulation followed by task specific training. This positive effect was observed immediately after the 12 sessions which were given over a period of four weeks of training, however, these positive results were not retained at three and six months of follow-up.[52] Both studies failed however to evaluate effects on somatosensory impairments and should also be considered as pilot studies, with an underpowered sample size.

Finally, future research could also consider implementing non-invasive brain stimulation techniques in sensorimotor rehabilitation as recent studies have highlighted the potential of non-invasive brain stimulation to complement and enhance rehabilitation effects in patients with stroke. A promising new technique called transcranial direct current stimulation (tDCS) elicits a constant weak electric current which has been shown to modulate motor cortex excitability by inducing alterations of neuronal resting membrane potentials in cortical tissue.[53,54] The attractive feature of tDCS in contrast to other brain stimulation methods is that it is safe, cheap and easy to apply and can be used during exercise.[55] Up to now, preliminary evidence[56] exist on the use of tDCS as a tool for priming the brain and enhancing neuroplasticity to support motor recovery in the arm and hand post stroke, however, the effect of tDCS on somatosensory recovery post stroke remains unexplored.

In this doctoral project we were not able to investigate treatment strategies for sensorimotor rehabilitation. However, two important findings from our studies need to be considered. First, our cross-sectional study (chapter 3), showed that in patients with neglect, the association between somatosensory and uni- and bimanual motor outcome is moderate to strong, whereas only low to moderate in the no-neglect group. This finding can be important when delineating sensorimotor rehabilitation strategies, as patients with neglect might benefit from other types of treatment. It is already shown in the literature that TENS applied over the hand muscles has a positive effect on the recovery of neglec[57,58] and other studies reported the beneficial effect of TENS on the recovery of motor function in the chronic phase post stroke.[51,52] Therefore, future studies are needed to evaluate the efficacy of somatosensory electrical stimulation of the arm and hand on motor outcome, both in patients with and without neglect in the different phases post stroke. Second, results from the cross-sectional study reported in chapter 5 showed the association between specific brain lesions and somatosensory dysfunction. However, up to now it remains unclear whether behavioural changes in response to sensorimotor therapy is a reflection of neurological recovery in the brain, which might be objectified using advanced brain imaging techniques in the future.

4. Conclusion

This doctoral project made an important contribution to the field of stroke rehabilitation by increasing our understanding about long-term motor and functional outcome post stroke and secondly about somatosensory impairments in the upper limb. More specifically, the findings of this doctoral project provide knowledge into the prevalence and distribution of impairments in different somatosensory modalities, as well as into the association with motor outcome and activity limitations. Finally, our brain imaging study contributes to the field of translational neurorehabilitation as it provides first insights into the neural correlates of somatosensory processing. Further elaboration of the current comprehension is recommended to offer more in-depth understanding of somatosensory deficits post stroke and to provide a sound base for therapeutic interventions aiming to improve sensorimotor outcome in the arm and hand post stroke.

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SUMMARY

Stroke is a leading cause of long-term disability, and therefore, considered as a major health burden globally. Following stroke, a variety of signs and symptoms occur, depending on the location of the brain lesion. Most commonly, patients experience unilateral muscle weakness in the face, arm or leg contralateral to the brain lesion. Additionally, an altered sensation or numbness in the face or limbs, speech disturbances and cognitive problems after often reported post stroke. In the literature, considerable agreement exists about the typical pattern of recovery for impairments and disabilities up to six months post stroke, irrespective of the type and amount of therapy. Detailed long-term motor and functional recovery patterns, measured up to several years after stroke rehabilitation, have received less attention.

Approximately 70% of stroke survivors experience impairments in the upper limb. As a consequence, upper extremity functions, such as reaching, grasping, releasing and manipulating objects are hindered, often resulting in a non-use of the affected upper limb. Dysfunction in the upper limb post stroke can therefore significantly limit a person's level of activity and participation and warrants further consideration in stroke rehabilitation research. It is well established that somatosensory information contributes to the control of movement as it provides information about the current state of the body segments to plan actions and to correct on-going movements. Although an intact somatosensory functioning is important for motor control in healthy subjects, it remains unclear to what extent somatosensory impairments following stroke are related to motor impairments in the upper limb, and whether the strength of this association changes over time.

Therefore, the aim of this doctoral project was to provide more insights into recovery post stroke, in particular with regard to long-term motor and functional outcome and to somatosensory function in the upper limb.

In **Chapter 1**, the long-term time course of motor and functional recovery post stroke was defined in 532 patients between admission to different European rehabilitation centres and five years post stroke. Additionally, patient characteristics that influence long-term recovery were explored. Results of this study revealed a significant deterioration in functional and motor scores between six months and five years post stroke, with a return to the level of

motor and functional performance measured at two months. Increasing age and increasing stroke severity negatively affected long-term outcome and patients with intracerebral haemorrhage showed significant better arm function compared with patients with cerebral infarction during the entire study period.

The following four studies of this doctoral thesis concentrated on increasing our understanding about somatosensory impairments in the arm and hand post stroke, and their importance in motor and functional outcome of the upper limb.

Chapter 2 presented a systematic review of the literature regarding the association between somatosensory impairments in the arm and hand and upper limb impairments, activity and participation problems post stroke. Despite the large variability in results, this review showed that several somatosensory deficits are related to upper limb motor and functional performance after stroke, albeit only explaining a small amount of the variance in motor outcome.

In **chapter 3**, a cross-sectional study including 122 patients in the first six months post stroke, was reported. The aims were to map the prevalence and distribution of different somatosensory deficits in the upper limb, and to investigate whether visuo-spatial neglect is a confounding factor; and secondly to determine the association between several somatosensory impairments and motor impairment and activity limitations, both in patients with and without visuo-spatial neglect in the sub-acute phase post stroke. Results of this study showed that somatosensory deficits are common in the sub-acute phase post stroke, and that the presence of visuo-spatial neglect is associated with the presence and severity of different somatosensory and motor deficits.

Chapter 4 described a longitudinal study, including 32 patients assessed within the first week post stroke and at six months, in order to map the change in prevalence and distribution of different somatosensory deficits in the upper limb; and to determine the association between somatosensory impairments and motor impairment and activity limitations, both in the acute and chronic phase post stroke. Results of this study revealed that upper limb somatosensory impairments are common both in the acute and chronic phase post stroke.

Furthermore, this study showed that in the acute phase, there is little association between somatosensory impairment and motor impairment, whereas at six months, different somatosensory impairments are related to motor impairments and activity limitations.

In the last chapter **(chapter 5)**, a cross-sectional observational study, including 38 patients within the first week post stroke, was reported. The objective was to investigate the relationship between stroke lesion location and the resulting somatosensory deficit in the upper limb. Voxel-based lesion-symptom mapping showed that lesions in two core brain areas are associated with different somatosensory impairments: the sensory component of the superior thalamic radiation and the secondary somatosensory cortex.

In conclusion, this doctoral project made an important contribution to the field of stroke rehabilitation by increasing our understanding about long-term motor and functional outcome and about somatosensory impairments in the upper limb. More specifically, the findings provide knowledge into the prevalence and distribution of somatosensory impairments, as well as into the association with motor outcome and activity limitations. Finally, our brain imaging study contributes to the field of translational neurorehabilitation as it provides first insights into the neural correlates of somatosensory processing. Further elaboration of the current comprehension is recommended to offer more in-depth understanding of somatosensory deficits and to provide a sound base for therapeutic interventions aiming to improve sensorimotor outcome in the arm and hand post stroke.

SAMENVATTING

Een cerebrovasculair accident (CVA) is een belangrijke oorzaak van langdurige invaliditeit, en wordt daarom ook wereldwijd beschouwd als een ernstig belasting op de gezondheidszorg. Na een CVA kunnen heel verscheiden symptomen voorkomen, afhankelijk van de plaats van de hersenbeschadiging. Patiënten ervaren vaak spierzwakte of motorische problemen aan één kant van het lichaam namelijk in het gezicht, de arm of het been aan de tegenovergestelde zijde van de hersenbeschadiging. Daarnaast komen een veranderd of verdoofd gevoel in het aangezicht of de ledematen, spraakproblemen en cognitieve moeilijkheden vaak voor na een CVA. In de literatuur bestaat er consensus over het typische patroon van herstel tot op zes maanden na het CVA, onafhankelijk van de therapie die wordt aangeboden. Er is echter weinig geweten over wat er in de chronische fase, tot verschillende jaren na het CVA met deze patiënten gebeurt qua motorische en functionele mogelijkheden.

Ongeveer 70% van de patiënten ervaart problemen in de arm en hand na een CVA, met als gevolg een belemmering van het gebruik van de arm en hand tijdens het reiken, grijpen, weer loslaten en manipuleren van voorwerpen. Dit resulteert vaak in een situatie waarbij de arm en hand niet worden gebruikt in dagdagelijkse taken. Problemen in de arm en hand kunnen dan ook significant de activiteiten en participatie van de personen met een CVA belemmeren, en daarom is verder onderzoek nodig binnen het domein van de CVA revalidatie. Het is geweten dat somatosensorische- of gevoelsinformatie een bijdrage heeft in de controle van het menselijk bewegen, omdat het informatie geeft over de huidige stand van lichaamssegmenten om accuraat de beweging te plannen en correcties op bewegingen uit te voeren. Hoewel een intact somatosensorisch functioneren belangrijk is voor motorische controle bij gezonde personen, blijft het tot op heden onduidelijk of somatosensorische problemen ten gevolge van een CVA geassocieerd zijn met motorische problemen in het bovenste lidmaat, en of de sterkte van de associatie verandert doorheen de periode van herstel na het CVA.

Het doel van dit doctoraatsproject was daarom om meer inzichten te verkrijgen in herstel na CVA, meer specifiek in het lange-termijn herstel van motorische en functionele mogelijkheden, maar ook in somatosensorische problemen in het bovenste lidmaat.

In **hoofdstuk 1** werd het lange-termijn herstel van motorische en functionele vaardigheden onderzocht in 532 patiënten tussen opname in verschillende Europese revalidatiecentra en vijf jaar na het CVA. Bijkomend werd ook gekeken welke patiënten-karakteristieken een invloed hadden op het lange-termijn herstel. De resultaten van deze studie toonden een significante achteruitgang in functioneel en motorische mogelijkheden tussen zes maanden en vijf jaar na CVA, met een terugkeer naar het niveau van functioneren gemeten op twee maanden na het CVA. Een hogere leeftijd en een ernstiger CVA hadden een negatieve invloed op lange-termijn herstel, en mensen met een intracerebrale bloeding hadden een duidelijk betere armfunctie in vergelijking met patiënten met een ischemisch infarct.

De volgende studies van deze doctorale thesis concentreerden zich op het verwerven van nieuwe inzichten in somatosensorische problemen in de arm en hand na CVA en het belang van deze problemen in motorische en functionele mogelijkheden van het bovenste lidmaat.

De studie in **hoofdstuk 2** is een systematische review van de literatuur omtrent de relatie tussen somatosensorische problemen in de arm en hand met functiebeperkingen, activiteiten- en participatieproblemen in het bovenste lidmaat. Ondanks de grote variabiliteit in resultaten toonde deze systematische review aan dat verschillende somatosensorische problemen geassocieerd zijn met motorische en functionele beperkingen van het bovenste lidmaat na CVA, al wordt maar een klein deel van de variantie in motorische uitkomst bepaald door het somatosensorische probleem.

In **hoofdstuk 3** wordt een cross-sectionele studie gerapporteerd waarin 122 patiënten werden geïncludeerd, allemaal binnen de eerste zes maanden na hun CVA. De doelen van deze studie waren enerzijds het in kaart brengen van de prevalentie en distributie van verschillende somatosensorische problemen in de arm en hand, en het onderzoeken van visuo-spatieel neglect als een geassocieerde factor, en anderzijds het bepalen van de relatie tussen somatosensorische problemen en motorische en functionele moeilijkheden in de arm en hand, zowel voor patiënten met en zonder neglect in de subacute fase na CVA. De resultaten van deze studie toonden aan dat somatosensorische stoornissen vaak voorkomen in de arm en hand na CVA en dat visuo-spatieel neglect geassocieerd is met de incidentie en de ernst van verschillende somatosensorische en motorische problemen in het bovenste lidmaat.

In **hoofdstuk 4** worden de resultaten van een longitudinale studie getoond waarin 32 patiënten werden geïncludeerd binnen de eerste week, en opnieuw gemeten op zes maanden na het CVA. De doelen van deze studie waren enerzijds het in kaart brengen van de verschillen in prevalentie en distributie van somatosensorische stoornissen in de acute en chronisch fase, en anderzijds het bepalen van de relatie tussen somatosensorische problemen en motorische vaardigheden en functioneel gebruik van de hand, zowel in de acute als de chronische fase na CVA. De resultaten toonden aan dat somatosensorische stoornissen vaak voorkomen, zowel in de eerste week als op zes maanden na het CVA. Verder toonde deze studie ook aan dat er een heel zwakke relatie is tussen somatosensoriek en motoriek in de acute fase, maar op zes maanden waren verschillende somatosensorische problemen wel duidelijk geassocieerd met motorisch en functionele problemen in het bovenste lidmaat.

In het laatste hoofdstuk **(hoofdstuk 5)** worden de resultaten van een cross-sectionele studie gerapporteerd, waarin 38 patienten werden geincludeerd binnen de eerste week na CVA. Het doel van de studie was het in kaart brengen van de relatie tussen de locatie van de hersenbeschadiging en het resulterende somatosensorische probleem in het bovenste lidmaat. Voxel-based lesion symptom mapping is een techniek waarmee deze relatie kan worden onderzocht. De studie toonde aan verschillende somatosensorische problemen voorkomen indien de hersenbeschadiging gelokaliseerd is in één van deze gebieden: de sensorische component van de superieure thalamische radiatie en de secundaire somatosensorische cortex.

Samenvattend kunnen we stellen dat dit doctoraatsproject een belangrijke bijdrage heeft geleverd in het domein van de CVA revalidatie door nieuwe kennis aan te brengen over lange-termijn herstel van functionele en motorische vaardigheden, en over somatosensorische problemen in het bovenste lidmaat na een CVA. De resultaten van dit doctoraatsproject geven nieuwe inzichten in de prevalentie en distributie van verschillende somatosensorische stoornissen, en in de relatie van deze stoornissen met motorische en functionele problemen in de arm en hand. Tot slot is er een bijdrage in het domein van de translationele neurorevalidatie door in de laatste studie de neurale correlaten te onderzoeken die belangrijk zijn in somatosensorische verwerking. Een verdere uitwerking van de huidige inzichten en kennis is nodig om een nog meer diepgaand begrip te vergaren omtrent somatosensorische problemen na een CVA, en om een goede basis te voorzien voor therapeutische interventies om deze somatosensorische problemen in de arm en hand aan te pakken.

BIJSTELLINGEN

Er zijn duidelijke gepubliceerde richtlijnen omtrent evidence-based CVA revalidatie. Maar, het is onduidelijk of deze richtlijnen ook in de klinische praktijk worden geïmplementeerd, wanneer patiënten in de chronische fase na een CVA behandeld worden.

Onderzoekers dienen rekening te houden met de kwetsbare situatie van acute, ernstig zieke patiënten die onder grote tijdsdruk moeten beslissen om deel te nemen aan onderzoek. Essentieel is om na te gaan of de patiënt het onderzoek goed heeft begrepen en of hij/zij in de mogelijkheid was om zelf beslissingen te nemen rond deelname.

Het peer-review proces is de standaard voor de evaluatie van de kwaliteit van publicaties in vaktijdschriften. Het weergeven van de namen van zowel de auteurs als de reviewers (open peer review) is een oplossing om de transparantie van dit proces te verhogen.

ABOUT THE AUTHOR

Sarah Meyer was born on June 11th 1987 in Leuven, Belgium. In 2005, she graduated from High School at Heilig Hart Instituut in Heverlee, Belgium. She graduated in 2010 cum laude as a Master in Rehabilitation Sciences and Physiotherapy (specialization neurological rehabilitation) at the KU Leuven, Belgium. After she graduated, she worked for Brunel Pharma for one year as a consultant at Merck Sharp and Dhome, Inc as a clinical trial assistant. In October 2011, she started as doctoral researcher at the Department of Rehabilitation Sciences in the Research Group for Neuromotor Rehabilitation at the KU Leuven under supervision of Prof. Geert Verheyden, Prof. Hilde Feys and Prof. Vincent Thijs. Her work focuses on recovery after stroke, with an emphasis on somatosensory impairments in the upper limb. Apart from her research work, she was involved in teaching activities in the Bachelor and Master program of Rehabilitation Sciences and Physiotherapy at the KU Leuven. In addition, she was elected representative of the assistants in the Faculty Council of the Faculty of Kinesiology and Rehabilitation Sciences of the KU Leuven.

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